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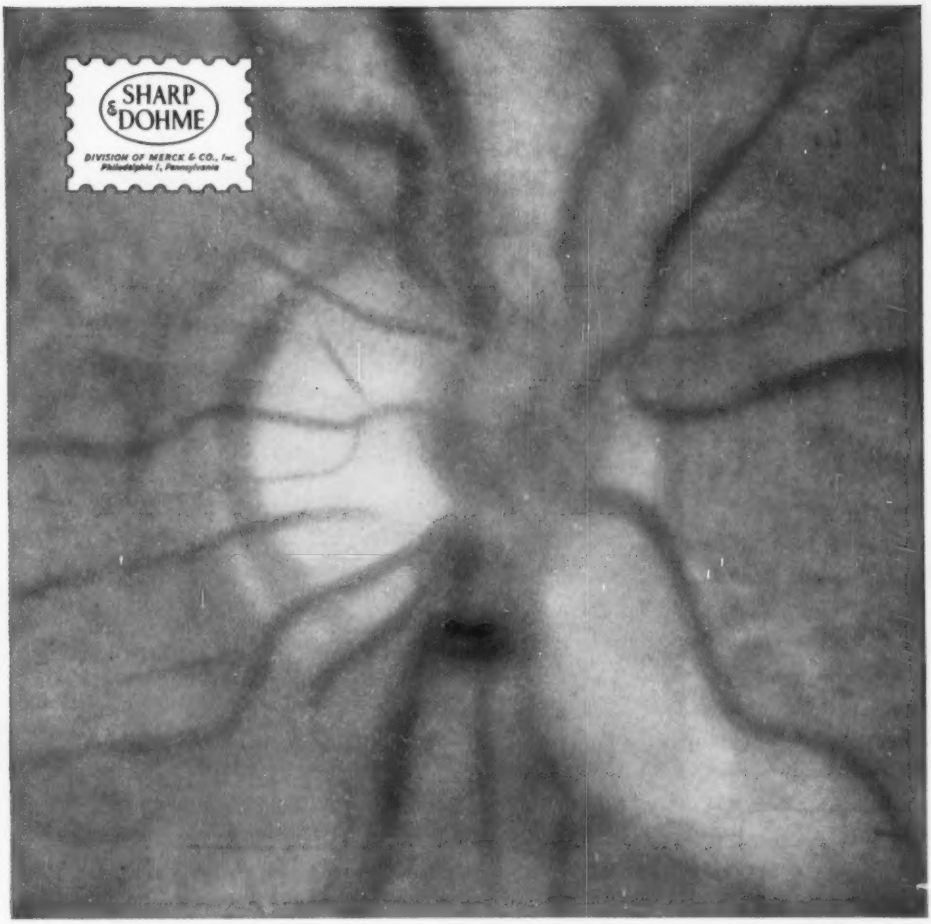

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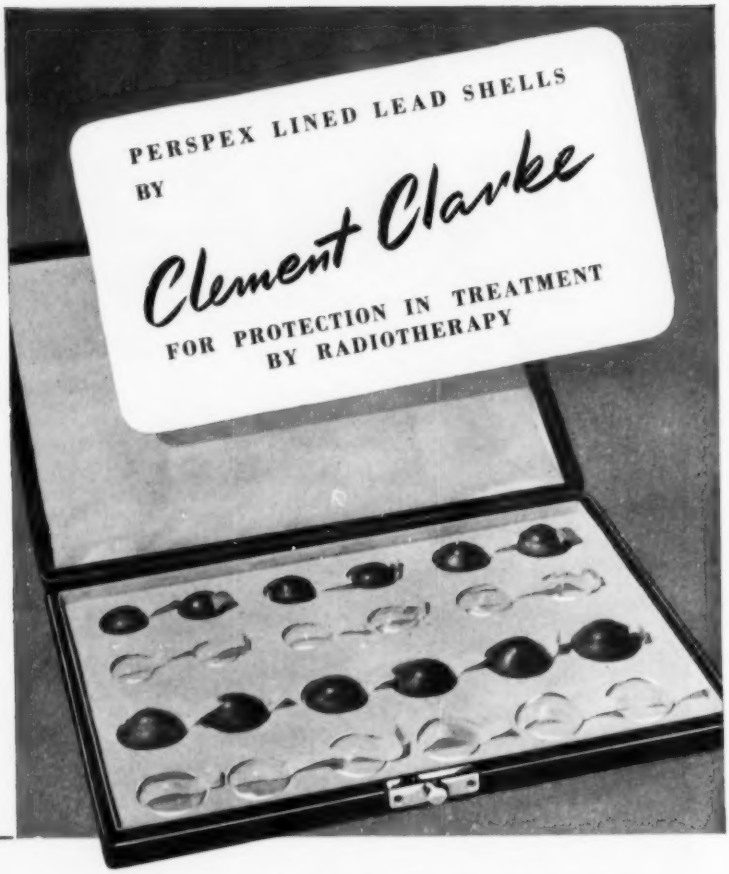

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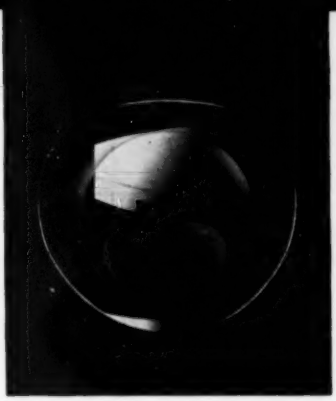

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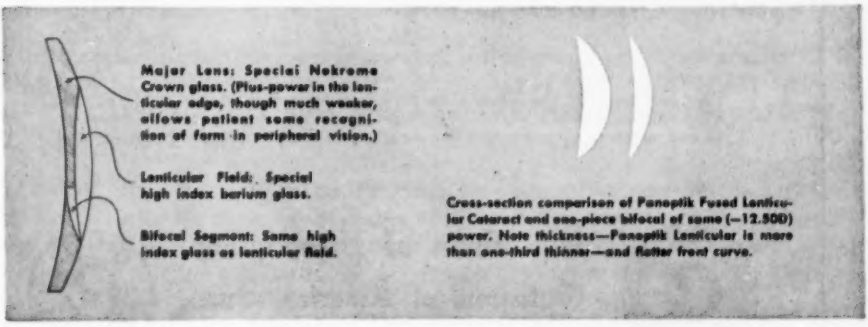
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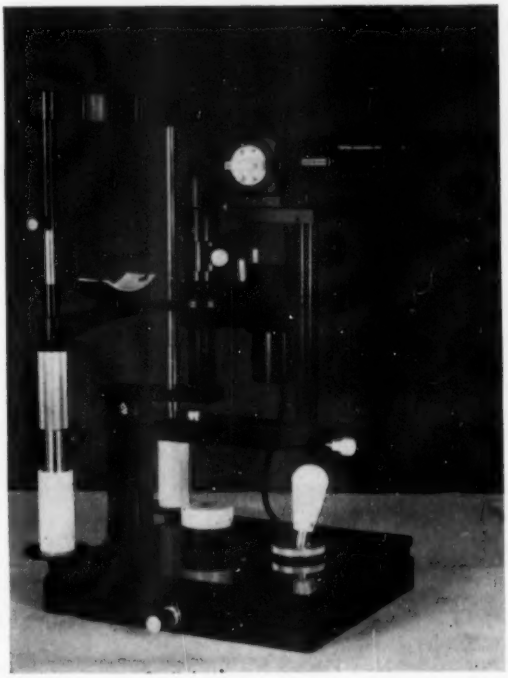

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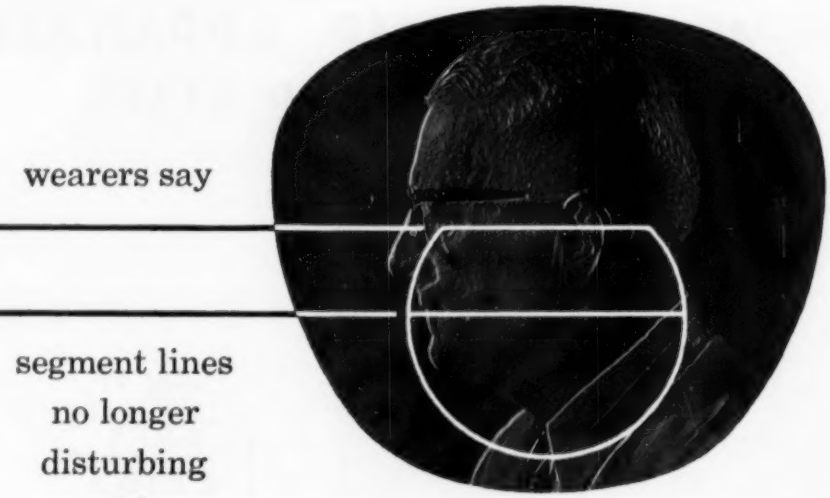

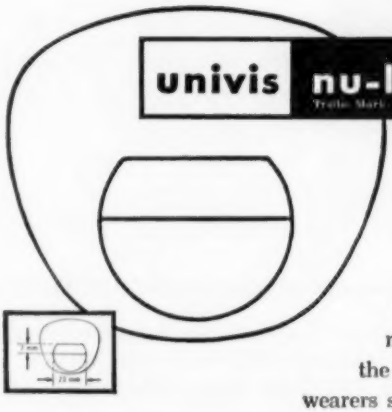

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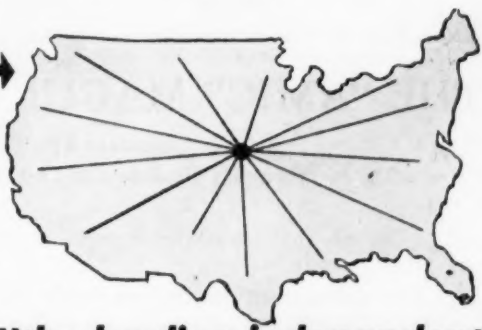

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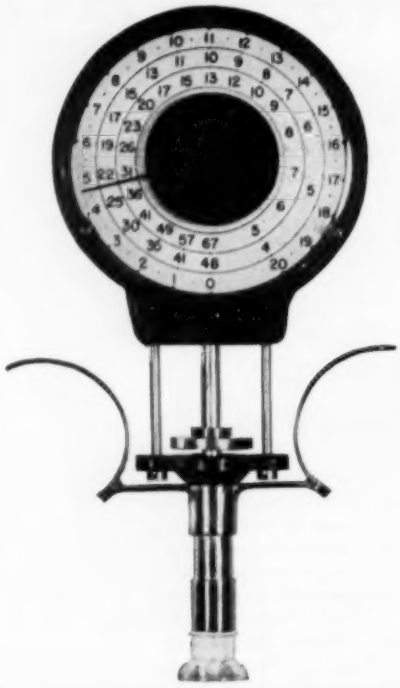

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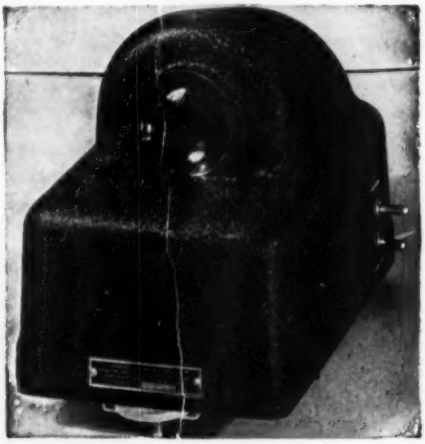

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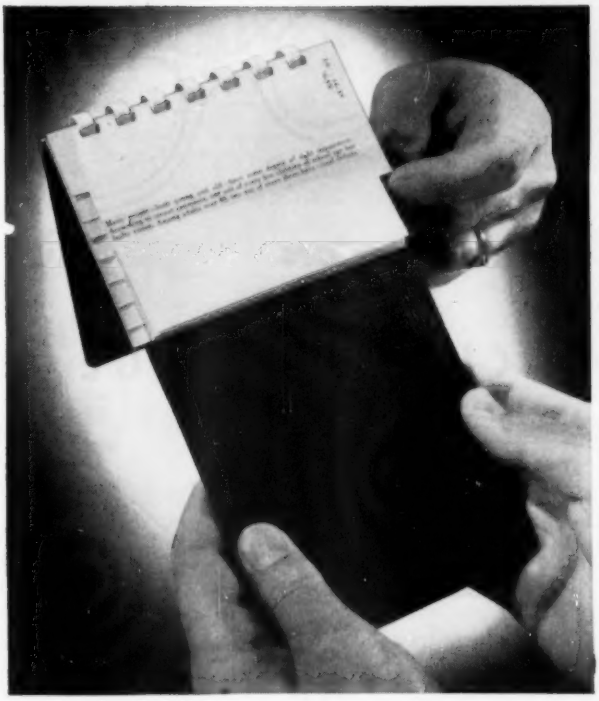

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VOLUME 52 AUGUST 1954 NUMBER 2

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Editorials

JOURNAL OF ALL-INDIA OPHTHALMOLOGICAL SOCIETY

A NEW OPHTHALMIC journal has appeared which gives promise of bringing us into closer relationships with our colleagues in the Far East. The first three issues of the *Journal of the All-India Ophthalmological Society,* with Dr. S. N. Cooper as the chief editor, reflects the great improvement in the teaching and practice of ophthalmology in India and fills the need for a really good Indian journal. In the past many excellent articles by Indian ophthalmologists were sent abroad for publication in foreign journals, owing to the lack of facilities for publication in India.

The first three issues are of a high standard, in both the material presented and the quality of workmanship. The paper and printing are good, and the illustrations are excellent. Many ophthalmologists in this country will be particularly interested in the reports of tropical ophthalmological diseases, such as amebiasis, leproma of the ciliary body, and toxoplasmosis in India. The editorial board of the *Journal* is doing an excellent job in further raising the standards of ophthalmology in India, and it is to be hoped that the journal will receive support from ophthalmologists in this country.

The editorial office is at Laud Mansion, 21, Queen's Road, Bombay 4, India. A subscription to this journal will give encouragement to the ophthalmologists in a country desperately in need of good eye care and be a friendly gesture from the West to the East.

FRANCIS HEED ADLER, M.D.

PATHOGENESIS AND TREATMENT OF OCULAR TUBERCULOSIS

ALAN C. WOODS, M.D.
BALTIMORE

I AM DEEPLY appreciative of the invitation to give the 16th de Schweinitz Memorial Lecture. In addition to the honor of the occasion, it gives me a sense of great personal gratification to pay public tribute to a man I honored, admired, and deeply loved, to a man to whom I owe a great personal debt. I knew George de Schweinitz from my childhood as a warm personal friend of my own father. In 1915 I came to Philadelphia to work under the late Richard Pearce in the Musser Laboratory for Research Medicine. Here, under the influence of de Schweinitz, I began investigation on ocular problems. For two years, up to the beginning of World War I, this association continued, and it was under his preceptorship that I began my clinical training. To say that he was an inspiring teacher is an understatement. He was much more than that. He combined the rare qualities of clear thinking, great knowledge, the highest intellectual honesty, and an enormous personal magnetism. During my years in Philadelphia, my friendship with him ripened and, after the war, continued up until his death. In those years I was a frequent visitor at 1705 Walnut St., and many weekends he visited us in Baltimore, always with his box of candy for Mrs. Woods and little presents for our children. And so I remember him as a great ophthalmologist, a distinguished and charming gentleman, and a dearly loved friend. To me he was one of the great figures of medicine, one to whom I owe an immeasurable debt, and one whose memory will always be sacred to me. It is therefore not only an honor but also a great personal pleasure and a privilege to deliver the lecture which bears his name. The subject I have chosen is one we often discussed together, and one that I know always interested him deeply.

I. PLEOMORPHISM OF THE LESION IN OCULAR TUBERCULOSIS

The most striking characteristic of ocular tuberculosis is the amazing pleomorphism of the lesions—the widely different clinical pictures produced in the eye by infection with the tubercle bacillus. These ocular lesions fall into four general groups, often merging one into the other. First, at one extreme, ocular tuberculosis may be little more than a foreign body reaction. An example of this is miliary tuberculosis of the iris (Fig. 1), in which there may be a minimum of inflammation and no tissue destruction, and the tubercles may be absorbed or hyalinized, leaving little or no residua. Second, the initial lesion may be characterized by sharp inflammation, but the process quickly becomes circumscribed and heals. Recurrence at or near the original lesion is frequent. Examples of this are the sclerokeratitis of

Delivered as the 16th de Schweinitz Memorial Lecture before the Section on Ophthalmology of the College of Physicians of Philadelphia, Nov. 8, 1953.

young adults and what de Schweinitz aptly termed "circumscribed plastic choroiditis" (Figs. 2 and 3). Third, tuberculous eye disease may be characterized by a long-drawn-out chronic course, with exacerbations and remissions and sometimes a slowly progressive tissue destruction. An example of this is the chronic tuberculous uveitis of adults (Fig. 4). Lastly, ocular tuberculosis may take on the picture of a violent, rapidly spreading inflammation with marked tissue destruction, necrosis, and caseation, sometimes terminating in rupture of the globe. Examples of this are the rapidly spreading chorioretinitis of children, young adults, and Negroes (Fig. 5) and the caseating tuberculomas (Fig. 6).

Fig. 1.—Miliary tubercles of the iris.

To understand these widely different tissue responses to infection with the same organism, one must understand the roles played by tissue hypersensitivity and by acquired resistance,* which factors largely determine the clinical picture and explain the pathogenesis of the lesion.

II. INFLUENCE OF HYPERSENSITIVITY ON THE TUBERCULOUS LESION

Koch himself was the first to recognize the hypersensitive phenomenon in tuberculosis. He noted that when a normal guinea pig was inoculated with tubercle

*The details of the experimental work dealing with hypersensitivity and resistance in tuberculosis, their independence, and the pathogenesis of the tuberculous lesion, together with complete bibliography, will be found in "The Pathogenesis of Tuberculosis," by Arnold R. Rich.[15]

bacilli there was at first only a minimal reaction at the site of inoculation and this reaction soon faded. Some 10 or more days thereafter a small macroscopic nodule appeared where the bacilli had been injected, the skin over this area became necrotic, and a progressive ulceration ensued, which continued up to the death of the animal. Synchronous with the development of this local nodule, there was manifest involvement and enlargement of the regional lymph nodes.

When a previously tuberculous guinea pig was similarly inoculated, there was an insignificant immediate reaction, but within 18 to 48 hours erythema and induration developed at the site of inoculation, followed by necrosis of the overlying skin and the development of a shallow ulcer. However, unlike the similar ulcer in the normal animal, this ulcer quickly healed. The regional lymph nodes were apparently

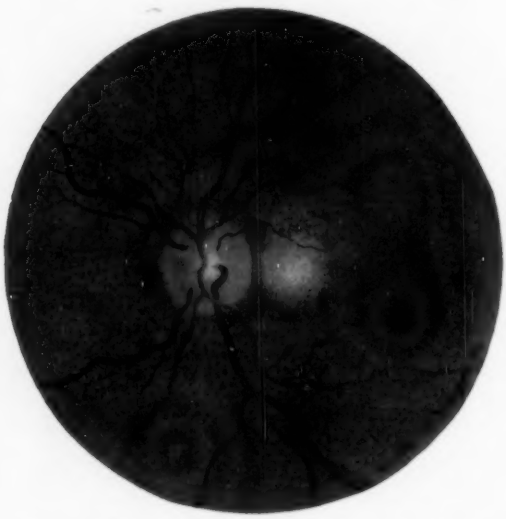

Fig. 2.—Circumscribed plastic choroiditis in young adult—early stages.

not infected. The local inflammatory reaction, coming on 18 to 48 hours after the injection of the bacilli, was soon widely known as the "Koch phenomenon," or the hypersensitive reaction.

Later investigations have added much to our knowledge of this reaction. As concerns Koch's original observations, it is known now that the local ulceration in both the normal and the tuberculous guinea pig is largely dependent on the number of bacilli injected. Likewise, in the tuberculous animal the regional lymph nodes are usually involved, but to a much less degree than in the normal animal. This difference is due to the inhibition of the spread and the propagation of the bacilli by the acquired resistance.

Further investigations on the reaction of normal and hypersensitive tissue to contact with tubercle bacilli showed there was no fundamental difference in the type of the inflammatory reaction. The difference is a quantitative rather than a qualitative one. In the hypersensitive tissue there is a prompt outpouring of polymorpho-

nuclear leucocytes and an early mobilization of mononuclear cells. If the amount of antigen (living or dead bacilli or tuberculin) injected is large, this early reaction may be intense, and, in addition to the erythema and induration which develops in 18 to 48 hours, there may also be necrosis and sloughing of the overlying skin. This ulceration rapidly heals. If living bacilli are injected, there is less involvement of the regional lymph nodes and fewer metastatic lesions than would develop in normal animals when similarly injected.

When a comparable dose of living bacilli is injected in normal tissue, there is, again, a primary gathering of the polymorphonuclear leucocytes and a later mobilization of mononuclears, but this cellular exudate is much scantier and its advent is delayed in comparison with the similar exudate in the hypersensitive tissue.

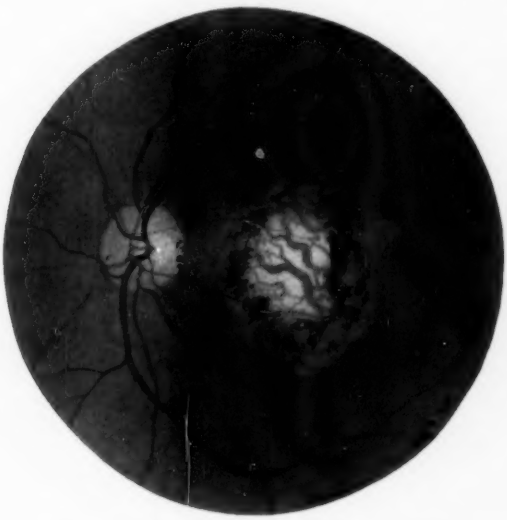

Fig. 3.—Circumscribed plastic choroiditis in young adult—healed stage.

Active inflammation and necrosis occur in the normal animal only after an incubation period of some days, during which time the invaded tissues become hypersensitive as a result of the infection. In the normal animal there is early involvement and enlargement of the regional lymph nodes. The bacilli then break through this lymphatic barrier, seed out rapidly throughout the system, and produce extensive metastatic lesions.

It is immediately evident that, while there is no fundamental difference in the type of inflammatory reaction produced in hypersensitive and in normal tissues by contact with the tubercle bacillus, there is an immense acceleration in the speed and intensity of the reaction in the hypersensitive host. Hypersensitivity disposes the tissues to a prompt inflammatory reaction, to necrosis, and to accelerated tubercle formation. In short, it accelerates and intensifies the destructive phase of the tuberculous lesion.

III. INFLUENCE OF RESISTANCE ON THE TUBERCULOUS LESION

Resistance is the ability of the body to destroy bacilli with which it comes into contact and to inhibit or alter the progressive growth and spread of the micro-organisms in the tissues. Thus the body escapes, either absolutely or relatively, the injurious effects of the toxic substances or tissue changes the organisms may produce. Resistance may be either natural or acquired. Natural resistance is the ability of the body to destroy the bacilli or inhibit their propagation on first contact with the micro-organisms. Acquired resistance is the increase in this bacteriocidal and bacteriostatic power which follows contact of the tissues with the infectious agent.

Fig. 4.—Chronic tuberculous uveitis.

Natural resistance in tuberculosis varies greatly in different species, in different races, and in individuals within the species. After infection, acquired resistance in tuberculosis develops in varying degrees in different persons. Clinical and experimental studies have shown that the resistance acquired from a prior tuberculous infection is not a solid immunity in the sense it confers an absolute protection against reinfection. Prior infection with the Mycobacterium tuberculosis confers a relative immunity on the host—relative in that it modifies the course of a reinfection. This acquired resistance is not constant, but is subject to fluctuations and may be depressed by a number of extraneous factors—malnutrition, physical and mental overstrain, intercurrent infections, trauma, endocrine disturbances, etc. It is probable that many of the clinical exacerbations and remissions so commonly seen in both systemic and ocular tuberculosis are the result of these fluctuations in resistance.

The mechanism whereby acquired resistance modifies the course of reinfection has been extensively studied. Its precise nature is, however, not yet fully understood. Undoubtedly there are two factors—humoral and cellular. The humoral factor is chiefly concerned with antibodies and may prepare the bacilli for phagocytosis. The cellular factor is concerned chiefly with the mononuclear cells, which phagocytose the bacilli. The phagocytic cells of a body with acquired resistance are able to destroy the bacilli better than the similar cells of a nonimmunized body. This may be related to a prior opsonization by the globulin antibody. The various studies on the nature of resistance in tuberculosis may be summarized as follows:

1. Acquired resistance inhibits the spread of infection from the site of inoculation.
2. It is instrumental in removing organisms which escape into the blood stream.

Fig. 5.—Sweeping chorioretinitis in Negro child.

3. It destroys many of the infecting bacilli, by preparing them for phagocytosis and by phagocytosis itself.
4. Whether by destruction of the bacilli or other means, it restrains the proliferation of the organisms.

The most important of these manifestations of acquired immunity is bacteriostasis—the inhibition of the spread of the bacilli and the suppression of their proliferation.

IV. INDEPENDENCE OF HYPERSENSITIVITY AND RESISTANCE

It was early recognized that the Koch phenomenon was accompanied by an increased resistance to reinfection; i. e., there was a rapid healing of the local lesion, an inhibition of the propagation and spread of the bacilli, with a decrease in both the involvement of the regional lymph nodes and the development of metastatic lesions. It was naturally concluded that these two simultaneously occurring phe-

nomena (the hypersensitive reaction and increased resistance to reinfection) were related or interdependent. Carrying this idea still further, it became widely accepted that hypersensitivity of the tissues was responsible for acquired resistance.

This view that hypersensitivity was related to acquired resistance, or was responsible for it, was challenged in 1929 by Rich and his co-workers. Then there ensued a variety of investigations on the hypersensitive reaction and acquired resistance.

These studies may be summarized as follows:

1. In syphilis, a chronic granulomatous disease, acquired resistance can be established in the experimental animal without the concomitant development of hypersensitivity.

2. In pneumococcal infections, acquired resistance can be separated from hypersensitivity by passive transfer.

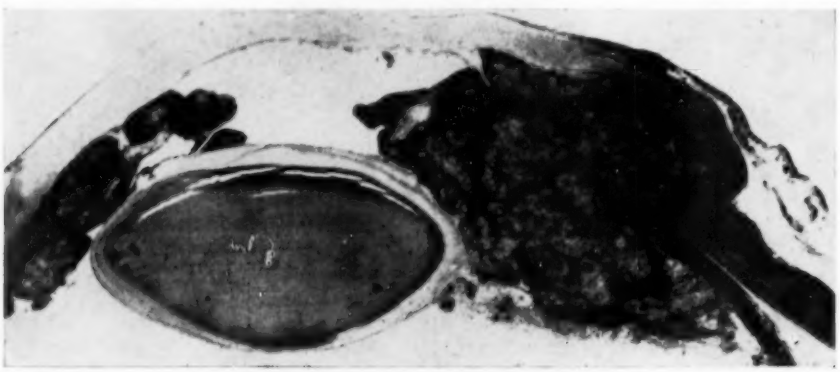

Fig. 6.—Tuberculoma of anterior ocular segment.

3. In tuberculosis (and other infections), the experimental animal with a prior infection can be completely desensitized to the specific micro-organism and to its soluble products without disturbing in any way the underlying acquired resistance.

As a result of these investigations, the following conclusions were drawn:

1. There is no correlation between the degree of hypersensitivity and the degree of acquired resistance, either in man or in experimental animals.

2. The hypersensitive inflammation in itself does not prevent the spread of the bacilli or protect against infection.

3. Acquired resistance is the factor which inhibits the spread of the bacilli and brings about their increased destruction.

4. Hypersensitivity and acquired resistance are independent immunologic phenomena and are in no way related one to the other.

V. PATHOGENESIS OF THE SYSTEMIC TUBERCULOUS LESION

As a result of these, and other, studies on the nature of hypersensitivity and acquired resistance, Rich reached the conclusion that after infection with the Myco. tuberculosis the nature of the resulting lesion was determined by the massiveness

and virulence of the inoculum, by the degree of hypersensitivity already present in the tissues, and by the amount of resistance present in the host. This, he expressed in a simple formula, now known as Rich's law. This formula is:

$$\text{Lesion } 00 \frac{\text{No. and Virulence of Bacilli} \times \text{Allergy}}{\text{Resistance}}$$

In this formula, *No.* indicates the number of bacilli in the infecting inoculum; *virulence,* the power of the specific strain to propagate in the tissues and produce progressive lesions; *allergy,* the degree of specific hypersensitivity present in the tissues; *resistance,* the amount of native and acquired resistance possessed by the host.

Thus, according to this law, infection with a small number of bacilli of low virulence in relatively insensitive tissues, with a high degree of native or acquired resistance, would result in a minimal, quickly healing lesion—little more than a foreign body reaction. At the opposite extreme, infection with a large number of virulent organisms in highly hypersensitive tissues with a minimum of resistance in the host would result in a progressive, destructive lesion with intense inflammation. Beween these two extremes there may occur a variety of lesions. In a patient with a definite tissue hypersensitivity and a high resistance, the immediate response to a moderate infection would be an exudative inflammatory lesion which might quickly be circumscribed, only to recur with a fall in the resistance. In persons with a moderate or low tissue hypersensitivity and a fair degree of resistance, infection with a moderate inoculum might result in a long-drawn-out chronic infection, with exacerbations and remissions, depending on the development of further tissue hypersensitivity and a rise or fall in the degree of resistance. Thus, this concept of the pathogenesis of a tuberculous lesion gives us a ready explanation for the pleomorphism of the lesion—the various clinical patterns which the same disease may assume.

Does this law hold true for ocular tuberculosis, in which the morbid process is walled off and confined in a tight, highly resistant corneoscleral envelope?

VI. PATHOGENESIS OF OCULAR TUBERCULOSIS

Beginning in 1938, a series of studies on experimental ocular tuberculosis was undertaken in the Wilmer Institute. These investigations were designed primarily to study the relation of ocular and cutaneous sensitivity under various conditions, to observe the effect of local tissue hypersensitivity and acquired resistance on the ocular lesion, and to provide fairly standardized lesions to test the efficacy of various therapeutic agents. During the course of these experiments, a number of observations were made which clearly indicate that Rich's law for the pathogenesis of a tuberculous lesion holds good in ocular tuberculosis. These observations may be summarized as follows:

1. The injection of a standardized dose of virulent human tubercle bacilli in the anterior chamber of a normal rabbit [1] produces initially nothing except a minimum traumatic and foreign body reaction, which lasts only a few days. The eye thereafter remains white and free of inflammation for a period of 10 to 14 days, after which time small, discrete tubercles appear in the iris or in the cornea. These progress slowly for the next one to two weeks, with only a low degree of inflammatory reaction. At the end of this period the inflammation increases and in a short time

becomes intense. Evidence of necrosis and caseation now appear; the eye gradually goes into buphthalmos and usually ruptures in 8 to 12 weeks. When the eyes of these rabbits were tested for hypersensitivity throughout the course of this experiment, it was found that the development of tissue hypersensitivity paralleled the onset of the acute inflammation.

2. When the anterior chambers of eyes of immune-allergic rabbits (animals previously infected systemically with human tubercle bacilli) were injected with a small dose of human tubercle bacilli, the eyes developed an acute inflammatory reaction within 18 to 48 hours.[2] This lasted three to five days and then faded. This inflammation had every appearance of a nongranulomatous iritis and was clearly a hypersensitive reaction produced in sensitized tissue by contact with the specific antigen—a local Koch phenomenon.

It was found that a much larger inoculum was required to produce lesions in the eyes of immune-allergic rabbits than was required in the normal rabbit. The small inoculum which produced lesions in the normal rabbit was innocuous in the immune-allergic animal. The bacilli were evidently destroyed by the resistance acquired from the previous systemic infection. Not until the dose was increased by 50 times did secondary ocular tuberculosis develop in the immune-allergic rabbit. When such a large dose was injected, after the subsidence of the allergic reaction, there was an incubation period of one to two weeks, after which the eyes developed a restrained tuberculosis. Only rarely was there acute inflammation, necrosis, or buphthalmos, and the eyes seldom ruptured. After a period of two to five months the disease burned out and the eyes recovered, with variable residua, from moderate to very slight scarring.

3. When immune-allergic rabbits were completely desensitized by repeated injections of tuberculin, and the eyes were thereafter injected with the increased dose necessary to produce lesions in the eyes of the immune-allergic rabbit, the eyes showed no reaction to the bacilli injected in the anterior chambers. The allergic reaction (or Koch's phenomenon) had been suppressed. The greatly augmented inoculum necessary to produce lesions in the hypersensitive-immune animal was still required to produce restrained lesions in the desensitized immune animals. The removal of the hypersensitivity had not affected the immune status.[3]

4. In immune-allergic rabbits with a low tissue sensitivity, both the Koch phenomenon and the intensity and severity of the secondary ocular tuberculosis were less than the reactions observed in similar rabbits with a high degree of tissue hypersensitivity.[3]

5. When immune-allergic rabbits were given injections in the anterior chambers of a still further increased dose of bacilli (10 to 50 times the minimum dose which produced the restrained lesions), the entire picture was reversed. These animals showed a violent and prolonged Koch reaction, which passed into actual secondary tuberculous disease without an intervening incubation period. This secondary ocular tuberculosis was characterized by intense inflammation and necrosis; buphthalmos and rupture of the globe were frequent.

The conclusions from these experiments may be summarized as follows:

A. In the normal animal acute ocular inflammation and necrosis accompany the development of ocular hypersensitivity and do not appear until such tissue hypersensitivity has developed as a result of infection.

B. Rabbits with a previous systemic infection from which they have recovered show a marked hypersensitivity to reinjection of bacilli in the eye and a greatly increased resistance to infection.

C. When the hypersensitivity is completely removed by desensitization with tuberculin, the rabbits are spared the Koch phenomenon when bacilli are injected in the anterior chambers. However, the underlying acquired resistance is entirely undisturbed; it still requires 50 times the dose used in normal rabbits to produce even a restrained tuberculosis in these desensitized immune animals.

D. A high degree of tissue hypersensitivity disposes the inoculated eye to acute and intense inflammation, while low tissue hypersensitivity disposes the inoculated eye to a low-grade and restrained inflammatory response.

E. When the inoculum is sufficiently large, the resistance of an immune-allergic animal may be completely overwhelmed, and the ocular disease assumes the malignant picture seen in the nonimmune animal, with acute inflammation, necrosis, caseation, and final rupture of the globe.

Thus, in ocular tuberculosis the factors which determine the type and course of systemic tuberculous lesion, as laid down in Rich's law, appear to hold true.

One other point relative to the pathogenesis of ocular tuberculosis must be mentioned. There is much confusion in the ophthalmological literature on the role of allergy in ocular tuberculosis, even to the point that it has been stated that all ocular tuberculosis is allergic in origin. Such an extreme view is misleading. It is true that phlyctenules are almost undeniably an allergic reaction of the cornea and that hypersensitivity to tuberculin and exposure to open tuberculosis are the most frequent cause of phlyctenulosis. It is true that the focal reaction in the eye to the systemic injection of an excessive dose of tuberculin is essentially an allergic reaction, although indicative of a former or active tuberculous focus in the eye. It is also true that during the course of any tuberculous infection of the eye the tissues may develop an augmented hypersensitivity to tuberculoprotein and absorption of tuberculin or tuberculoprotein from the local focus will cause a secondary allergic reaction superimposed on the basic granulomatous disease. However, with these exceptions, it is almost certain that all clinical tuberculous disease of the eye is the result of an actual invasion of the ocular tissues by the Myco. tuberculosis in living form. Bacilli have frequently been demonstrated in the eye by bacterial stains of sections and by transmission experiments. The failure to find them, or to demonstrate their presence in a tuberculous eye, is probably due either to technical difficulties or to actual destruction of the bacilli. In this respect the eye is no different from other tissues of the body; it does not show an independent allergic reaction unless a specific bacterial hypersensitivity has been produced by a prior or an active infection, and, like other tissues, tuberculous disease in the eye is produced by actual infection with the Myco. tuberculosis. Once such disease is established, the future course of the lesion may be profoundly influenced by tissue hypersensitivity.

VII. TREATMENT OF OCULAR TUBERCULOSIS

A. Nonspecific Therapy.—The treatment of ocular tuberculosis may be divided into nonspecific and specific procedures. Nonspecific treatment consists of a variety of procedures used by ophthalmologists to meet various local complications and to place the eye in a better condition to resist infection. Nonspecific treatment includes

the use of mydriatics to dilate the pupil and to increase circulation in the anterior ocular segment, the use of heat to allay pain and promote capillary dilatation, paracentesis to control tension and increase the antibody content in the re-formed aqueous, and adrenal cortex hormonal therapy to control an alarming acute inflammation. Phototherapy, once popular for its supposed secondary effect of relieving arteriolar spasm, is now less frequently used. Nonspecific protein treatment, the beneficial effect of which is probably due to stimulation of the adrenal cortex, is likewise largely supplanted by bouts of adrenocortical hormonal therapy, although it is still used as "shock" therapy in torpid inflammations.

The use of corticotropin, cortisone, and hydrocortisone in ocular tuberculosis requires special comment. As already emphasized, the ocular tissues may develop a high degree of tissue hypersensitivity as a result of the local infection. Once such hypersensitivity is established, a reaction with the tuberculoprotein from the local focus may produce an allergic reaction around the lesion. This may be manifested clinically by an acute exacerbation of inflammation in the anterior ocular segment or by an edematous reaction around a choroidal exudate. Thus, one is confronted with the picture of a nongranulomatous allergic process superimposed on a basic granulomatous lesion. An acute allergic reaction may be destructive and threaten the functional integrity of the eye by causing secondary glaucoma, or by necrosis of the retina. In such cases the use of adrenal cortex hormonal therapy is justified. In some manner it inhibits the inflammatory and destructive phase of the hypersensitive reaction. However, as soon as a secondary allergic reaction has been controlled, hormonal therapy should be tapered off and discontinued. There is now sound experimental and clinical evidence [4] that the continued use of hormonal therapy in ocular tuberculosis may be directly harmful and result in a spread of the local disease. It tends to inhibit phagocytosis, fibrosis, and encapsulation of the lesion, all of which are fundamental factors in the healing process. Therefore the use of adrenal cortex hormonal therapy is contraindicated in ocular tuberculosis except for the immediate control of a secondary inflammatory allergic reaction, which in itself may be destructive and threaten the functional integrity of the eyes.

B. Specific Therapy.—Specific therapy in ocular tuberculosis is based upon the already outlined concept of the pathogenesis of the local lesion. It is designed (1) to conserve and augment the resistance which induces bacteriostasis, inhibits the proliferation, promotes the phagocytosis of the bacilli, and thus limits the spread of the lesion; (2) to remove the fatal tissue hypersensitivity which promotes acute inflammation and tissue destruction, and (3) to attack the invading bacilli—to immobilize and destroy them by specific bacteriostatic and bactericidal agents.

These objectives may be approached as follows:

1. Enhancement of Resistance: The enhancement of resistance is the time-honored cornerstone in the therapy of tuberculosis and, despite the recent development of specific antituberculous agents, is still of the highest importance. What means are available to preserve and enhance acquired resistance?

It is known that the inoculation of children with an attenuated organism (BCG) results in an increased resistance to later infection and a decreased incidence of active, adult tuberculosis in the vaccinated group. It has also been found that various chemical fractions of the tubercle bacillus—the proteins, carbohydrates, and lipids—will incite antibody formation. However, these are not procedures which can be

used to stimulate the development of resistance in an already infected human being. In 1893 Trudeau [5] stated that the direct production of an acquired immunity to tuberculosis in man was a therapeutic ideal which would probably never be attained. Unfortunately, this is as true today as it was 60 years ago. In the efforts to enhance resistance, the physician today is reduced to those measures which may place the body in the most favorable environment to preserve what resistance may already be present and to facilitate the production of further acquired resistance. Such measures are essentially the proper regulation of the patient's hygiene.

Since it is known that malnutrition unfavorably affects the development of resistance, it is important that the diet be adequate and properly balanced and any vitamin deficiency be supplied. Physical and mental overstrain must be avoided. Indeed, it is remarkable how simple bed rest and proper diet may sometimes favorably affect a severe tuberculous uveitis in a run-down, overworked, and undernourished patient. As far as possible, the patient must be protected from intercurrent infections. Chronic and debilitating foci of infection should be sought for and eradicated. If there is any obvious endocrine disturbance, it should be compensated for as far as possible. This is about all one can do to enhance resistance, and, although it is obviously simple, its importance cannot be gainsaid. Despite the claims of the Davos school, it is highly improbable that high altitude therapy per se has any effect on ocular tuberculosis. The same can be said for sanatorium treatment. All either of these can do is to place the patient in a happier environment, calculated to make easier the regulation of general hygienic measures.

2. Removal of Tissue Hypersensitivity: There is no evidence that any chemical constituent of the tubercle bacillus has any inherent toxicity for normal tissue. Similarly, the soluble products of the bacillus which occur in the medium in which the micro-organism propagates are nontoxic for the normal body. On the other hand, there is convincing evidence that tuberculoprotein, other chemical constituents of the bacillus, and tuberculin are highly toxic for the hypersensitive host. The destructive phase of the tuberculous lesion is due to the toxic action of these substances in hypersensitive tissue. It has repeatedly been shown experimentally in both systemic and ocular tuberculosis that if the experimental animal is completely desensitized by repeated injections of tuberculin the introduction of living or dead bacilli, or of purified protein derivative, in the skin or anterior chamber of the eye will not produce local inflammation or any toxic reaction. Therefore, if the tissues of the eye can be completely desensitized, the destructive phase of the tuberculous lesion will be suppressed, even though living, propagating bacilli remain therein. This is well illustrated by the following experiment.[6]

A large number of normal rabbits were infected systemically with a human tubercle bacillus. After a period of four months they had recovered from the mild disease which results from the infection and had developed a well-marked hypersensitivity to tuberculin and an increased resistance to reinfection. They had become "immune-allergic." They were then inoculated in the anterior chamber of one eye with a proper dose of the same human tubercle bacillus. The injected eyes developed the usual Koch phenomenon, which subsided within three to four days. After an incubation period of two to three weeks, all the eyes developed the usual restrained ocular tuberculosis seen in the immune-allergic animal. When the disease was well established, the rabbits were divided into two groups of equal size. One group was left untreated as controls, while the second group was given repeated large doses of tuberculin to desensitize them as rapidly as possible. Twenty-four hours after the first injection the diseased eyes of the treated rabbits all showed a violent exacerbation of inflammation—a typical focal reaction. This reaction

subsided within a few days, and all further injections of tuberculin were taken without local or focal reactions. After the subsidence of the focal reaction, the inflammation in the eyes faded, the tubercles became circumscribed and slowly absorbed, and within five weeks the eyes of these treated rabbits were free of inflammation and without clinical evidence of active tuberculous disease. During this period the eyes of the untreated, control rabbits developed the usual progressive but restrained disease, which finally burned out after a period of six months.

When the treated group had received tuberculin for five weeks, the disease in the control group was at its height. The control group was then given one injection of tuberculin. The diseased eyes of these animals all developed a violent focal reaction, which subsided in a few days. Thereafter the tuberculous disease progressed in the the usual manner.

At the end of the experiment, when the disease had burned out in the control group and was completely inactive in the treated group, the eyes of both groups were injected with PPD to test the ocular sensitivity. The eyes of the controls showed a definite reaction, while the eyes of the treated rabbits were nonreactive. The treatment with tuberculin had resulted in a practically complete desensitization of the eyes of the treated group, and, synchronous with this desensitization, there had been a subsidence of inflammation and a rapid control of the ocular infection by the resistance acquired as a result of the prior systemic infection. This experiment is shown graphically in Figure 7.

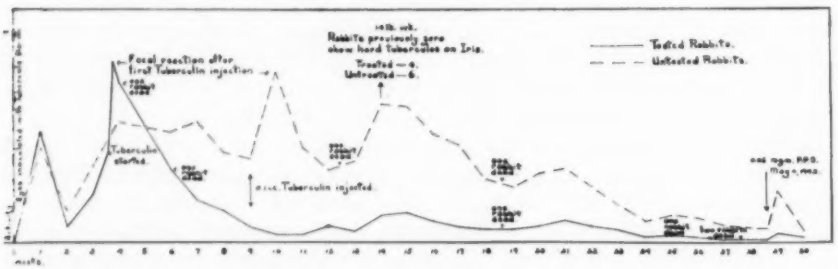

Fig. 7.—Graph indicating course of ocular tuberculosis in untreated immune-allergic controls and in desensitized rabbits.

How may such desensitization be achieved in clinical patients? When tuberculin was first discovered by Koch, it was received with the hope that it might be almost a specific in the treatment of tuberculosis. It was soon evident, however, that tuberculin as then used did more harm than good in the long run. Its use was gradually abandoned except among ophthalmologists, where it maintained a few wavering adherents. In the light of our modern knowledge of the pathogenesis of the tuberculous lesion, it appears that much of the unfortunate early results stemmed from the manner in which tuberculin was used. As long as it was believed that the allergic reaction was responsible for resistance, and was therefore a favorable phenomenon, the obvious method of using tuberculin was to employ it to promote slight allergic reactions around the lesion. This was the "perifocal" concept. It was realized, however, that if the perifocal reaction was at all intense, it might be harmful. It was necessary, therefore, to give a dose just sufficient to stimulate a low-grade reaction, and insufficient to evoke a severe one. However, the margin between a beneficial subclinical perifocal reaction and a destructive focal reaction is small, and severe ocular reactions were frequent. Further, when tuberculin was used under this concept, it was believed that when a favorable effect was observed the goal of treatment had been attained and tuberculin should immediately be stopped to avoid the risk of a harmful focal reaction.

The demonstration by Rich in 1929 that allergy and resistance were independent phenomena and that allergy was responsible for the destructive phases of the tuberculous lesion completely altered this "perifocal" concept for the use of tuberculin and introduced the "desensitization" concept. Under this idea, tuberculin should be used not to provoke subclinical perifocal reactions but as a desensitizing agent. Thus, it should be given in small doses well below the patient's point of reactivity and the dose increased only as the point of reactivity recedes. Furthermore, once the lesion is apparently healed and the patient desensitized, tuberculin should not be stopped, but should be continued. It has been abundantly shown that if tuberculin is stopped when desensitization has been accomplished, the tissue hypersensitivity will often return, and with the return of sensitivity acute inflammatory lesions may follow.

The full details of the technique for desensitization have been given elsewhere. They may be summarized here as follows: The Saranac dilutions of tuberculin are used. Denys Bouillon Filtrate (DBF) is the preferred preparation. The initial dose is never greater than 0.1 cc. No. 8 (0.00001 mg.), and a smaller dose is used in the extremely hypersensitive patient. The dose is first given every four days and is slowly increased until 0.8 cc. of No. 5 is reached. Thereafter injections are given once a week. Treatment is thus continued until a dose of 0.5 cc. of a No. 2 dilution (50 mg.) is reached. This is regarded as the maximum and is continued as a maintenance dose at weekly intervals for a two-year period. At that time, if the patient is insensitive to an intracutaneous test dose of 0.1 mg. and the eye in inactive, tuberculin is discontinued. The patient's cutaneous reactivity, however, should be redetermined at six-month intervals, and should there be a return of cutaneous sensitivity, treatment is recommenced, regardless of the inactivity of the eye.

The following precautions are observed:

1. If there is any local reaction at the site of injection, the dose is dropped three levels, and only again increased when the smaller dose is taken without local reaction.

2. If there is any evidence of a focal reaction in the eye, the dose is reduced to one-tenth that previously given. If this is taken without reaction, the dose is thereafter increased in the usual manner. If there is still an ocular reaction to the smaller dose, the amount of the next injection is again cut to one-tenth that causing the reaction.

The clinical results of this desensitization therapy have been thoroughly good in the control of inflammation and the prevention of acute inflammatory relapses. Prior to the introduction of specific chemotherapy and antibiotic therapy, desensitization with tuberculin was the therapeutic mainstay. The objections to such therapy are the relatively long time (four months to a year) required to achieve desensitization, the inability to accomplish desensitization in the occasional patient, and the fact that while it greatly diminished the severity of any recurrence, desensitization does not prevent it. Nevertheless, since there is approximately a 20 to 25% failure rate as concerns recurrence, even with the best antibiotic therapy and chemotherapy, desensitization with tuberculin is still indicated in the hypersensitive patient with ocular tuberculosis. The relation between ocular and cutaneous sensitivity has been discussed elsewhere.[2]

C. Direct Attack on the Tubercle Bacilli.—From the time of the discovery of the Myco. tuberculosis as the cause of tuberculosis, investigators have sought for agents which would exert a direct action on the organism, inhibit its growth, and encompass its destruction. The details of this search have included the use of colloidal gold salts, of various aniline dyes coupled with bactericidal mercuric salts, of various sulfones, of various chemotherapeutic agents, and, finally, of antibiotics.

The results of this long search may be summarized as follows: On the negative side, while colloidal gold salts probably have some weak bacteriostatic effect on tubercle bacilli, the side-reactions attendant upon their clinical use have occasionally been so severe that they are now rarely used. The use of aniline dyes and various combinations of dyes with other agents have been disappointing despite the ability of these dyes to penetrate tubercles. The use of sulfanilamide, while encouraging in guinea pig tuberculosis, has been without results in clinical tuberculosis.

On the positive side, within the last few years several therapeutic agents have been discovered with a specific action against the Myco. tuberculosis. These agents are (*a*) the antibiotics streptomycin and dehydrostreptomycin and (*b*) certain synthetics. The bacteriostatic and bactericidal actions of these substances have been extensively studied in experimental animals and in clinical patients with both systemic and ocular tuberculosis. The story of their use in systemic tuberculosis is well known and does not concern us here.

The study of their action in experimental ocular tuberculosis has contributed considerably to our knowledge. The eye presents a unique site for the study of a therapeutic agent, permitting a day-by-day evaluation of the progression or regres-

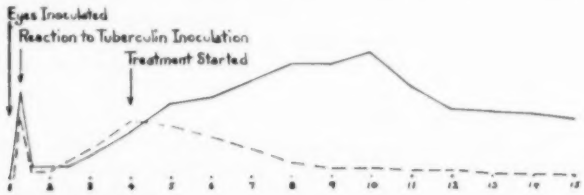

Fig. 8.—Graph illustrating course of ocular tuberculosis in untreated immune-allergic controls and in immune-allergic rabbits treated with streptomycin only.

sion of the lesion under attack. The different picture and course of ocular tuberculosis in the normal and in the immune-allergic rabbit permits tests of varying severity. The use of normal rabbits provides a severe test for the bacteriostatic and bactericidal action of a therapeutic agent, while the use of immune-allergic rabbits provides a less severe test but gives a more prolonged period in which to observe the effect of the agent under study.

Effect of Streptomycin Alone in Experimental Ocular Tuberculosis: Streptomycin and its derivative dehydrostreptomycin are the only antibiotics as yet discovered with a marked specific action on tuberculosis. The various other antibiotics thus far studied have either a minimal bactericidal action or no action whatsoever in ocular tuberculosis.

Preliminary studies showed that streptomycin alone had an inhibitory and therapeutic action in ocular tuberculosis in the normal rabbit, where it operates without the aid of any acquired resistance. This was to be expected in view of the previously demonstrated bacteriostatic and bactericidal power of this agent. In the "immune-allergic" rabbit, where there was the added factor of acquired immunity, the therapeutic result was more marked.[7] Figure 8 shows graphically the results of treatment with streptomycin alone in the immune-allergic rabbit. While the

clinical effect was marked, nevertheless, the failure rate (recurrences, histological evidence of active disease, and the demonstration of viable bacilli in the eyes after cessation of treatment) was a full 50%.

Effect of Synthetics in Experimental Ocular Tuberculosis: The synthetics with an antituberculous action thus far discovered are (*a*) certain diaminodiphenylsulfones; (*b*) the aminohydroxybenzoic acids, chief of which is paraaminosalicylic acid (PAS); (*c*) the thiosemicarbazones, and (*d*) a pyridine carboxylic acid derivative, isoniazid. The action of the thiosemicarbazones has been studied extensively in Germany, and it is reported that they have a marked therapeutic action in clinical ocular tuberculosis. Unfortunately, all compounds of this group have a high toxicity for bone marrow, the liver, and the kidney, and for this reason have been studied and used sparingly, or not at all, in this country.

The action of the sulfones, PAS, and isoniazid in experimental ocular tuberculosis is summarized as follows:

(*a*) The sulfones. Three diaminodiphenylsulfones with a specific action in tuberculosis have thus far been synthesized. These are known as sulfoxone sodium

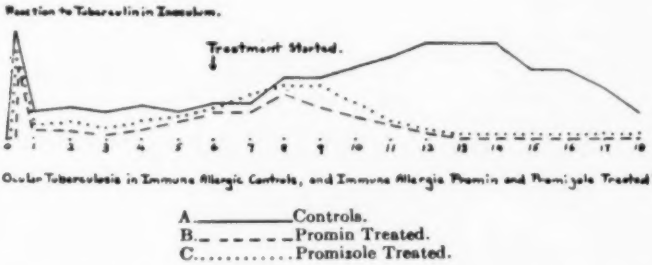
Reaction to Tuberculin in Immunes.
Treatment Started.
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Course of Ocular Tuberculosis in Immune Allergic Controls, and Immune Allergic Promin and Promizole Treated Rabbits.
A _____ Controls.
B. _ _ _ _ _ Promin Treated.
C. . . . . Promizole Treated.

Fig. 9.—Graph illustrating course of ocular tuberculosis in untreated immune-allergic controls and in immune-allergic rabbits treated with glucosulfone sodium and with thiazolsulfone.

(Diasone), glucosulfone sodium (Promin), and thiazolsulfone (Promizole). Sulfone sodium is too toxic for ordinary use and has not been studied in ocular tuberculosis. Glucosulfone sodium has an inhibitory action about similar to that of thiazolsulfone, or perhaps somewhat greater. However, it is much more toxic than thiazolsulfone. Thiazolsulfone has only a weak action in ocular tuberculosis in the normal rabbit, where it operates without the acquired resistance factor.[8] Its therapeutic action in the immune-allergic rabbit, where acquired resistance is present, is more marked.[9] However, in the immune-allergic rabbit the failure rate (recurrences, etc.) was at least 60%. The sulfones appear to owe their therapeutic properties as much to a bacteriostatic action as to a bactericidal one. Figure 9 shows graphically the action of glucosulfone sodium and thiazolsulfone in the immune-allergic rabbits.

(*b*) Paraaminosalicylic acid. Paraaminosalicylic acid alone has a well-marked action in experimental ocular tuberculosis in the normal rabbit,[10] although the overall failure rate with PAS alone was at least 75%. The action of PAS in the normal rabbit is shown in Figure 10.

(*c*) Isoniazid (isonicotinic acid hydrazide). This is the latest addition to the chemotherapeutic agents with a specific antituberculous action. Although first syn-

thesized by Mayer and Malley in 1912, it was neglected until its resynthesis by Fox in 1952, when its antituberculous action was discovered. It has an extremely narrow spectrum, limited almost solely to the Myco. tuberculosis. The greatest drawback to its use is the frequent development of bacillary resistance to the drug. A recent study [11] indicates that in man 11% of the treated patients developed such a bacillary resistance at the end of the first month of treatment, 52% at the end of the second month, and 71% at the end of the third month.

Isoniazid has a marked bacteriostatic and practically no bactericidal action in ocular tuberculosis in the normal animal.[12] Its action has been studied in the normal rabbit, but not as yet in the immune-allergic rabbit. This bacteriostatic action is

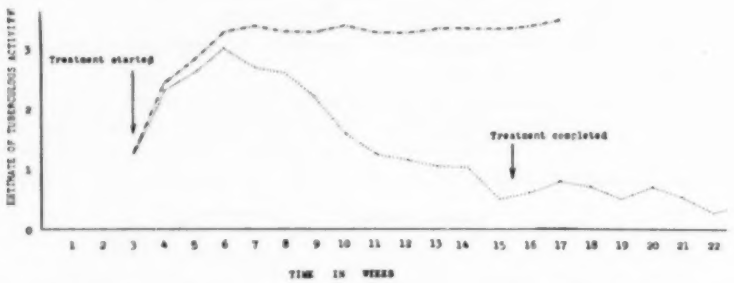

Fig. 10.—Graph illustrating course of ocular tuberculosis in (*a*) untreated normal controls, and (*b*) in normal rabbits treated with paraaminosalicylic acid alone.

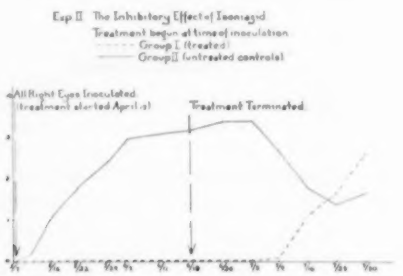
Exp II The Inhibitory Effect of Isoniazid
Treatment begun at time of inoculation
Group I (treated)
Group II (untreated controls)
All Right Eyes Inoculated
(treatment started April 1st)
Treatment Terminated

Fig. 11.—Graph illustrating inhibitions of lesions in normal animals treated with isoniazid from time of inoculation of eyes.

much more marked than that of either thiazolsulfone or PAS. When normal rabbits were treated with isoniazid from the time of inoculation of the eyes (Fig. 11), all evidences of tuberculous disease were suppressed during the period of treatment and for 21 days thereafter. Three weeks after treatment was terminated all the treated rabbits developed the malignant picture of ocular tuberculosis seen in the normal rabbit and within three weeks were as bad as the controls.

When normal rabbits were treated with isoniazid after the disease was well established in the eyes, a definite improvement in the ocular picture was noted within six days. This improvement steadily continued, until after 40 days of treatment the eyes were free of any clinical evidence of tuberculosis. In the meantime the disease in the controls had progressed to buphthalmos, necrosis, and rupture of

the globe. When treatment was terminated, the treated rabbits were kept under observations for four to five months. A recurrence was first noted on the 56th day, and thereafter, during the period of post-treatment observation, 66% of the treated rabbits developed severe recurrences (Fig. 12). When these relapsing rabbits were again treated with isoniazid, it was found that in almost two-thirds of them such renewed treatment was without effect. They appeared to have developed a bacillary resistance to the drug.

This study indicates that isoniazid has a marked bacteriostatic action and probably owes its therapeutic effect to this property. The 100% late development of ocular lesions after cessation of early treatment, and the 66% recurrences after

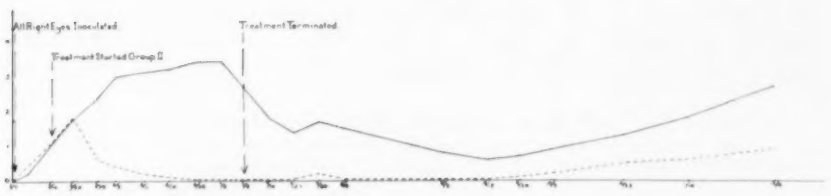

Fig. 12.—Graph illustrating therapeutic action of isoniazid administered to normal rabbits after development of ocular lesions.

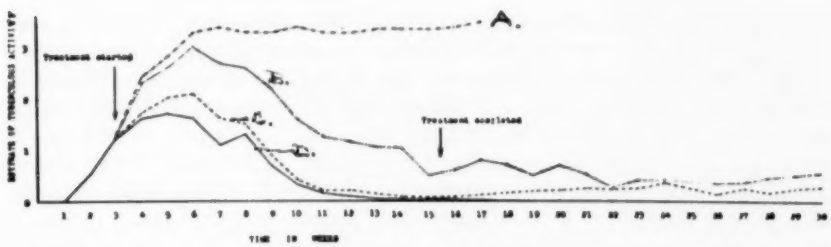

Fig. 13.—Graph illustrating course of ocular tuberculosis in normal rabbits: (*A*) untreated controls, (*B*) rabbits treated with PAS only, (*C*) rabbits treated with streptomycin and PAS, and (*D*) rabbits treated with streptomycin and thiazolsulfone (Promizole).

treatment was stopped (when apparent clinical cure had been attained), would indicate that isoniazid has little or no bactericidal action. The rabbits which did not relapse probably owe their escape from recurrences to the development of acquired resistance rather than to any bactericidal action of isoniazid.

Effect of Combined Treatment in Experimental Ocular Tuberculosis: Primarily, the use of either thiazolsulfone or paraaminosalicylic acid as an adjuvant with streptomycin appears to decrease the development of bacillary resistance to streptomycin. When organisms were recovered by culture from the eyes of either normal or immune-allergic rabbits receiving the combined treatment, the recovered bacilli were still sensitive to streptomycin.

Secondly, when either normal or immune-allergic rabbits were treated with streptomycin and either thiazolsulfone or paraaminosalicylic acid as an adjuvant, the over-all therapeutic response to such combined treatment appeared somewhat greater than would have been expected from a mere additive effect and suggested a synergistic action.

As in other experiments, the response to treatment was greater in the immune-allergic rabbit, where the additional factor of acquired resistance was present, than in the normal rabbit, where this factor was absent. In the normal rabbit [13] the symptomatic response to combined treatment was noted about the 14th day of treatment and the eyes were free of clinical evidence of active tuberculosis after 10 weeks' treatment (Fig. 13). In the immune-allergic rabbit, which is the experimental analogue of the human with ocular tuberculosis, a regression of the lesions was noted somewhat earlier and the eyes were clinically inactive after eight weeks' treatment.[7]

While the increased action of combined therapy was moderately apparent on clinical observation, it was more evident when the eyes of the treated rabbits were examined histologically for evidence of active tuberculosis and tested for viable bacilli by culture and transmission experiments. Thus, in the normal rabbit the

Failure Rate with Specific Therapy in Experimental Ocular Tuberculosis
(Recurrences, persistence of viable bacilli and histologic evidence of active disease)

Type of Experimental Rabbit	Sulfones Alone	PAS Alone	Streptomycin Alone	Streptomycin Plus Sulfones	Streptomycin Plus PAS
Normal	100%	75%	Not done	60%	60%
Immune-allergic	75%	Not done	50%	20%	Not done

final failure rates with sulfones and PAS alone were, respectively, 100% and 75% (counting recurrences, histological evidences of activity, and demonstrated viable bacilli), while with combined therapy the rate was reduced to 60%. In the immune-allergic rabbit the failure rates with sulfones and streptomycin alone were, respectively, 75% and 50%, while with combined therapy the rate was cut to 20%. These results are shown in the accompanying Table. It seems quite probable that streptomycin and either thiazolsulfone or PAS may well act on different phases of the intermediary metabolism of the tubercle bacillus, thus giving a synergistic action. Thiazolsulfone and PAS appeared to have about equal therapeutic effects when used as adjuvants with streptomycin (Table).

Studies on the added use of isoniazid as an adjuvant to streptomycin in the treatment of experimental ocular tuberculosis have not as yet been completed. It is quite probable that such combined use may further decrease the failure rate. It will be interesting to see what effect such combined use will have on the bacillary resistance which so often develops to each agent when they are used separately.

Clinical Use of Antibiotics and Synthetics in Ocular Tuberculosis: When the therapeutic action of streptomycin had been demonstrated in experimental ocular tuberculosis and when it had been shown that this action was enhanced by the use of thiazolsulfone as an adjuvant and that bacillary resistance to streptomycin was thus minimized, clinical patients with ocular tuberculosis were treated with this combined method.

Since the diagnosis of ocular tuberculosis is always more or less presumptive, in the first clinical study[14] the only patients treated were those for whom there appeared to be no doubt of the accuracy of the diagnosis. The dosage used in these patients was 0.5 mg. of streptomycin twice daily and 1.5 gm. of thiazolsulfone every six hours around the clock. Treatment was at first continued over a minimum period of 84 days. Later, as it became evident that a good therapeutic response was usually obtained earlier, the treatment period was shortened to a minimum of 42 days, provided that a satisfactory result was obtained in this time. Of the 14 patients so treated in the first series, a dramatic therapeutic result was obtained in every patient. The improvement was first noted from the 9th to the 21st day of treatment, usually about the 14th day. Thereafter evidences of active disease steadily diminished, until after about five weeks' treatment the majority of the eyes appeared free of inflammation and activity. A few cases required six to eight weeks for a similar result to be obtained. The results in these patients were as striking as those in the experimental animals. In every case clinical improvement was apparent before any toxic side-effects occurred. Toxic reactions, slight tinnitus, vertigo, nausea, and urticaria were observed in about 60% of the patients treated, but in none were these manifestations serious and in every case they disappeared after stopping either the streptomycin or the thiazolsulfone. After cessation of treatment, in an observation period of four years, there have been recurrences of the ocular disease in approximately 25% of these patients.

When it was demonstrated that PAS had a therapeutic spectrum approximately equal to that of thiazolsulfone, that it had a similar synergistic action with streptomycin, and that it likewise had the same inhibitory effect on the development of bacillary resistance to streptomycin, it was substituted for thiazolsulfone as the adjuvant. Paraaminosalicylic acid was given in doses of 3 gm. every six hours. Only occasionally were toxic effects referable to the drug noted, and these were limited to gastric irritation, and occasionally slight urticaria. No appreciable difference was noted in the therapeutic action of streptomycin plus PAS and that of streptomycin plus thiazolsulfone. There has been the same incidence of recurrences. PAS has the advantage of giving slightly less toxic reactions.

When the marked bacteriostatic action of isoniazid was demonstrated, it seemed logical to add this drug to the therapeutic armamentarium—to combine the bacteriostatic action of isoniazid with the bacteriostatic and bactericidal action of streptomycin and PAS or thiazolsulfone. The clinical results which have followed this therapeutic regime have been more than gratifying. A definite therapeutic effect is observed sometimes as early as the fourth day, and rarely later than the eighth day. The final outcome has been the same—in cases of clear-cut ocular tuberculosis all evidences of activity have usually disappeared after five to six weeks' treatment, only extremely severe cases requiring more prolonged therapy. Isoniazid is given orally, usually 300 mg. in divided doses for the first five days and thereafter 150 mg. daily. Only rarely were any side-effects attributable to isoniazid noted with this dosage.

The use of isoniazid early in treatment appears to be of value in the diagnosis of ocular tuberculosis. As noted elsewhere, in the absence of fluids to examine for bacilli and of tissue for biopsy and animal inoculation, and with the inability of roentgenography to give any diagnostic help, the diagnosis of ocular tuberculosis is always more or less a presumptive one. In many patients the clinical picture,

the course of the disease, and the associated findings are so characteristic that there is little doubt of the accuracy of the diagnosis. There are, however, many patients in whom, while the general picture is highly suggestive, it is impossible to rule out other etiologic factors. In these patients the diagnosis of ocular tuberculosis is at best a tentative one. Since isoniazid has a spectrum limited almost specifically to the Myco. tuberculosis, its use adds the "therapeutic trial" to the diagnostic armamentarium. In a case of doubtful etiology, an early response to isoniazid and streptomycin is probably indicative of the tuberculous nature of the ocular disease, and absence of a therapeutic response is evidence against such an etiology.

The last change made in the specific therapeutic regime for ocular tuberculosis concerns streptomycin. Recent studies on the action of streptomycin in tuberculosis have shown that a dose of streptomycin of 1.0 gm. every second day is about as efficacious as the dose of 1.0 gm. daily. The incidence of side-effects is lessened with the decreased dosage. It has further been shown that if a mixture of equal parts of streptomycin and dehydrostreptomycin is given, the toxic effects on the vestibular and auditory nerves are less than those observed when the full dose of either antibiotic is given alone. Such a preparation of equal parts of streptomycin and dehydrostreptomycin is now available commercially. This has been used during the last year in a dosage of 1.0 gm. every second day. With this preparation the occurrence of side-effects referable to streptomycin has been minimal.

The present regime for the chemotherapy-antibiotic therapy in ocular tuberculosis is the administration of a mixture of dehydrostreptomycin and streptomycin, 1.0 gm. every second day by intramuscular injection; paraaminosalicylic acid, 3.0 gm. every six hours orally, and isoniazid, 100 mg. orally three times daily for the first five days and 50 mg. three times daily thereafter. Treatment is continued for a minimum of 42 days, and longer if a full therapeutic result has not been obtained. If there is no response to this therapy within three weeks, the situation is again reviewed and the original diagnosis of ocular tuberculosis is questioned. If any symptoms referable to the vestibular or auditory nerves develop, the streptomycin is omitted, and its administration is resumed cautiously only when such symptoms have cleared. If there is any gastric distress, fever, or cutaneous eruption, the PAS is stopped and thiazolsulfone substituted. If such symptoms continue, the isoniazid is omitted. The use of these precautions has given a satisfactory control of the low-grade side-effects. In a few cases, after a holiday of a week or more from the offending drug, it has been possible to resume therapy without the further development of toxic reactions. In no case have toxic manifestations resulted in any permanent damage, and in only one case, where severe urticaria developed and persisted during any treatment, was it necessary to abandon all specific therapy.

SUMMARY

Ocular tuberculosis, despite its circumscription in the tight corneoscleral envelope, does not differ in its pathogenesis from any other systemic tuberculous lesion. The character of the lesion is largely dependent on the number and virulence of the invading bacilli; the inflammatory and destructive phases of the lesion are determined by the degree of tissue hypersensitivity already present or which may develop, and the immobilization and destruction of the bacilli and the circumscription of the lesion are accomplished by the native or acquired resistance present.

This concept of the pathogenesis of ocular tuberculosis gives us our clue to the treatment of the disease. The first step is to conserve and promote the native and acquired resistance. There is little that can be done on this point other than regulation of the personal hygiene, proper diet, control of intercurrent infections, elimination of foci of infection, and any other therapy indicated by the individual needs of the patient.

The second point is the estimation of the degree of tissue hypersensitivity present. If there is a high degree of tissue reactivity to tuberculin or PPD or evidences of acute inflammation in the eye, the sensitivity of the ocular tissues to tuberculoprotein may be assumed to be high. Desensitization therapy with tuberculin is then indicated. It should be undertaken with the realization that it is a long and tedious process, that it will take months to achieve tissue desensitization, and that once such desensitization is attained, tuberculin must be continued for a long period to prevent a return of the hypersensitivity. The dose of tuberculin should always be below the point of reaction of the individual patient, and all local and focal reactions should be avoided. Such desensitization therapy is indicated for the reason that should the patient have a recurrence, such recurrence will take place in insensitive tissue and the destructive phases of the tuberculous lesion be avoided.

The final, and most important, step is the direct attack on the bacilli. To this end there are available isoniazid, streptomycin, and paraaminosalicylic acid or thiazolsulfone (Promizole) as adjuvants. This specific therapy consists of a mixture of streptomycin and dehydrostreptomycin, 1.0 gm. every second day; paraaminosalicylic acid, 12 gm. daily, and isoniazid, 300 mg. daily in divided doses. After five days the dose of isoniazid may be reduced to 150 mg. Treatment should be continued for a minimum period of 42 days, and longer if a full therapeutic response is not obtained. The patient should be carefully watched for any side-effects, and if such are noted the drug probably responsible is either omitted entirely or the dose greatly decreased. If paraaminosalicylic acid is believed responsible, thiazolsulfone may be substituted.

With such a regime, in cases of undoubted ocular tuberculosis, some clinical improvement is usually noted within two weeks. The absence of any therapeutic response within three weeks throws doubt on the validity of the original diagnosis. Even with a favorable initial response and complete control of all clinical evidence of activity, there are recurrences of the ocular disease in about 25% of the patients adequately treated. For this reason, desensitization therapy is indicated to lessen the severity of such recurrences and prevent the destructive phases of the lesion.

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BASIS OF STEREOSCOPIC VISION

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IT IS NOW generally accepted that stereoscopic depth localization arises solely from the disparity between the images in the two eyes. There is still uncertainty, however, regarding the role played by certain factors associated with the disparate stimuli that are also necessary for the emergence of the stereoscopic experience.

The most important of these factors pertain to simultaneity and retinal locations. Must the two stimuli be received by the two eyes at the same time, and must they fall on specific horizontally associated retinal elements? According to the literature, the term "simultaneity" cannot be taken literally. Stereopsis can be experienced from disparate images presented successively first to one eye and then to the other.[1] However, under such conditions we are probably dealing with after-images, for it has been shown repeatedly that stereopsis can be obtained from disparate after-images induced in each eye separately.* But the stereoscopic experience from such images apparently lasts only as long as the after-images themselves persist.[4] In this sense, therefore, we can say that the stereoscopic depth is experienced only as long as the disparate retinal elements involved are in an excited state at the same time.

The problem with respect to retinal location concerns the question whether the disparate stimuli, at least in part, must fall on specific horizontally associated disparate retinal elements. In 1873, two students of Donders, van der Meulen and van Dooremaal,[5] reported their observations from an experiment that bears on this question. They used the well-known Hering "falling sphere" test.[6] In this test, through a horizontal slit aperture, the eyes view a vertical thread (plumb line) as fixation object, and the subject observes whether a small sphere dropped by an assistant appears to fall in front of or behind the fixed plumb line. This device provides a sensitive test for stereopsis, and it avoids most of the empirical motives or clues to depth perception.

These experimenters, however, placed a prism of sufficient strength, base down, before one eye so that the image of the slit seen by that eye would be entirely above the actual slit seen by the other eye. The images of the plumb line are still used as the fixation object, although it is not clear how the separated images of the plumb line could be used as a true fixation object, except through a voluntary control of the convergence of the eyes on the part of the observer keeping the two images aligned. When a small sphere is now dropped near the plumb line, the path of its

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* References 2 and 3.

fall will not be seen simultaneously by the two eyes. The upper half of the path of the fall will be seen by one eye; the lower half of the path will be seen by the other eye.

The experimenters reported that in spite of there being no instant when both eyes saw the sphere, the path of the falling sphere nevertheless could always be correctly judged as nearer or farther than the plumb line. Thus, they concluded (in translation):

> Stereoscopic depth is to be conceived not as a direct physiologic phenomenon, but as a psychic one; that is, the depth is produced by a psychophysical process. In this experiment the stereoscopic depth experience arises solely through the means of imagined prolongations of the half-images, which then in the usual stereoscopic manner would be referred to horizontally corresponding (or disparate) retinal points.

Now, if this depth sense were always the case, "we should have to classify binocular depth perception among the gestalt perceptions. The central factor involved in this perception would be a behavior acquired by the experience in the life of the individual, an unconscious, effectual reaction, such as we have already learned to think of as the basis for gestalt perception." [7]

As far as I can learn, this experiment has never been subjected to a critical analysis. However, Hofmann must have repeated it, for he stated that the depth impression from this falling sphere under these conditions, while sufficiently convincing, is nevertheless not very obvious.[7] In nonius or vernier type experiments for the determination of the horopter, where the upper halves of the test lines are seen by one eye, and the lower halves by the other, no author save Burian [8] has suggested that any stereoscopic depth was experienced from such separated images. Certainly, evidence from experiments designed to test this spatial factor specifically should bear directly on the problem of whether stereoscopic vision rests on a neuroanatomic and physiologic basis, or whether, as van der Meulen and van Dooremaal and others have concluded, it is fundamentally a psychophysical phenomenon.

This paper will describe experiments which, under controlled conditions and improved instrumentation, extend the basic experiment performed by van der Meulen and van Dooremaal. The results confirm their experiment only in a very restricted sense. The results show, on the contrary, that specifically horizontally associated disparate retinal elements must be stimulated for the emergence of a true stereoscopic depth experience.

APPARATUS

The instrument used was a further modification of the haploscopic device previously described in the study of the precision and validity of stereoscopic depth.[9] Figure 1 is a schematic drawing of the apparatus used for the present experiments. The position of the subject's head was held accurately by a sturdy head rest and a wax bite. The head of the subject was carefully adjusted to the instrument so that the eyes would be level with respect to the apertures. The wax bite and four-button head rest assured that the eyes would return to the same position when the head was temporarily removed from the apparatus and later returned to it. The subject fixated a brightly illuminated spot (1 mm. diameter) on a sheet of thin plate glass 50 cm. from the eyes, which were symmetrically converged. The subject also saw the images of a reference and a test object by

reflection from suitable mirrors (50-50 transmission-reflection). Secondary reflections from the back surfaces of the mirrors were reduced by coating. The reference object consisted of a polished thin steel drill rod (about 4 cm. in length), mounted vertically and seen by reflection from a fixed mirror. The position of the rod could be adjusted so that when seen stereoscopically it could be located at any position before or behind the fixation point and at any peripheral angle up to about 8 degrees. This rod when suitably illuminated produced a brilliant vertical line.

The test object either was a drill rod identical to that used for the reference line or was a falling sphere, such as that used in the Hering test. One or the other of these test objects was seen by reflection from the mirror combination nearest the eyes (Fig. 1). These two mirrors, when rotated about vertical axes (A)——(A)

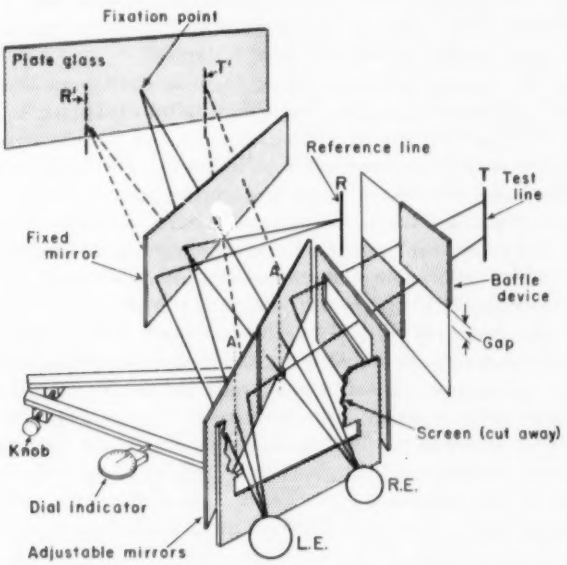

Fig. 1.—Instrument of haploscopic type used to study stereoscopic depth perception with specially screened images of the test object. The falling sphere (Hering) test could be substituted for the test line illustrated here.

through small angles in directions opposite each other, produced a change in the disparity between the images of the test object and, accordingly, produced a change in the stereoscopic depth of the test object relative to the fixation point or to the reference line. The mirror rotations were controlled by a handwheel through suitable levers and a screw. The angle of disparity was always symmetrical about a given lateral position of the test object when on the Vieth-Müller circle.† The geometric angular disparity is zero when the test object is at this position.

A dial indicator showed the amount the mirrors had been turned and therefore showed the angular disparity of the images of the test line in minutes of arc. An estimated $\frac{1}{5}$ scale division corresponded to 6 seconds of arc angular disparity. The

† References 10 and 11.

test object could also be set at any peripheral angle by adjusting the arm support.† This experimental arrangement made possible a wide range of disparities of the images of the test object. Within this range the images did not change angular size or brightness or change their optical distance; that is, they did not become blurred as the stereoscopic depth changed. Empirical clues to spatial localization from the test object were thus virtually eliminated.

The drill rods were illuminated by lamps on the same electric circuit, so that both could be illuminated continuously, or momentarily when a time switch was inserted in the circuit. The switch could be operated either by the experimenter or by the subject.

The falling-sphere attachment consisted of a suitable reservoir for holding the spheres (steel ball bearings 1/16 in. in diameter) and a mechanism for releasing these. A long cable release, when pushed, caused a sphere to fall into a cup below the field of vision of the subject. The angular extent of the fall was 10 degrees, and the time of the visible fall was less than 0.1 second.

The binocular visual field was restricted to the fixation point and to the images of the reference and test objects by suitable horizontal slit apertures and a septum. The fixation point and the images of the reference and the test objects were seen against a large, evenly illuminated white background. The individual backgrounds for the reference and test objects were, however, completely black. The principal aperture screen was also illuminated so as to have the same brightness as the background. The experiment was otherwise conducted in a semidarkened room.

The important modification of the apparatus for the present experiments was the interposition of a baffle device in front of the test object, to screen that object differently to the two eyes (Fig. 1). The two baffle plates were made of thin square pieces of blackened metal, with the inner edges beveled. These plates were attached to a right-angled two-directional rack-and-pinion part of a microscope mechanical stage. This stage, in turn, was mounted on another horizontal rack-and-pinion unit. By means of the three movements, each of the two baffle plates could be adjusted to screen any portion of the test object to each of the eyes. In particular, the vertical separation of the plates, that is, the gap, could be accurately set by means of scales and verniers. Through this gap the two eyes could simultaneously see a central portion of the test line. The baffle plates were adjusted as necessary so that one eye saw the entire upper portion of the line above the gap but not the lower, and the other eye saw the lower portion below the gap but not the upper. The side aperture (which subtended an angle of 3.5 arc degrees), used with the drill test rod, was cut from black cardboard. This aperture screened the upper and lower ends of the lines from the eyes. Thus throughout the experiments, each eye saw the same length of the test line, including, but independent of, the gap through which both eyes could see the same central portion of the line.

The adjustment of the baffle plates corresponding to the "zero" gap was important. The procedure was for the subject, his head held in the instrument, to adjust the lower baffle plate vertically so that the reflected image of its edge (temporarily illuminated) coincided with the center of the fixation point. With an illuminated sheet of paper beyond the test object, the subject then adjusted the upper baffle plate vertically until its lower edge and the upper edge of the lower baffle just cut out light between the two. Care was taken not to raise the level of the general illumination, because the size of the pupil is a factor in the determination of the

"zero" position of the baffles. An alternate method was to use the illuminated line itself instead of the paper background. The vernier readings of the two scales for this zero position were then recorded. For a given gap each baffle was then displaced one-half the gap width symmetrically from this zero position. The adjustment and maintenance of this zero gap constituted one of the principal sources of error.

Two subjects were used in this study. One had had considerable experience in stereoscopic observations. In the experiment he used a +1.25 D. sphere before each eye to correct for partial presbyopia and to eliminate an esophoria. The other subject had had only limited experience in making stereoscopic observations. Although about 0.50 D. myopic in each eye, he used no glasses in the experiment. Both the method of adjustment and the method of constant stimuli were used to obtain measures of stereoscopic sensitivity.

PROCEDURE AND RESULTS

I. *Reference Line Seen in the Frontoparallel Plane; Short Exposures of Reference and Test Lines.*—First, the experiments will be described in which the drill rods, and therefore the reference and test objects as bright lines, were used. The subject, with head in the instrument, adjusted the reference line so that it would appear at the same distance as the fixation spot and 1.5 arc degrees to the left of it. He then adjusted the arm that supports the test line so that its stereoscopic image would appear 1.5 arc degrees to the right of the fixation spot. Thus, the disparity of the images of the reference line, η_0, with respect to the fixation point, was substantially zero. The reference and test stereoscopic images were placed on either side of the fixation point to prevent any possible association between the half-images of these objects and the images of the fixation point, such as occurs in Panum's limiting case experiment. When the operator or the subject turned the handwheel controlling the rotation of the mirrors, and thereby changed the angular disparity of the images of the test line, the test line appeared to move stereoscopically in front of or behind the plane of the fixation point and of the reference line.

For this experiment, the electric time switch in the electric circuit was set so that when the control button was pushed, both the reference and test lines were illuminated for 0.2 second. This exposure was short enough to prevent any serious influence of eye movements and at the same time was long enough to assure an adequate stimulus for stereoscopic depth perception.

With the method of adjustment, the subject, while carefully fixating the fixation spot, adjusted the knob to a position chosen at random, exposed the lines, and judged whether the test line was seen as farther or nearer than the reference line. The knob was adjusted again in the direction to reduce the error in depth, and another judgment was made. By the procedure of successive approximation, adjustments were continued until the subject felt that the test line and the reference line appeared at the same distance. The dial indicator reading was then recorded. This process was repeated 10 times, with adequate rest periods. Between observations the subject was asked to look away from the fixation point to the white area of the aperture screen in order to help break up any after-images, perhaps any memory of the image positions, and to lessen fatigue. From the data obtained, the angular

disparities corresponding to the average setting and to the standard deviation of the settings were computed. The stereoscopic sensitivity bears an inverse relationship to the stereoscopic threshold, which, in turn, is proportional to the standard deviation.

The gap between the baffle plates was set at the beginning for 4 mm., which corresponds to a vertical visual angle of 40 minutes of arc. Within this angular length both eyes saw the same portion of the test line. Above and below this gap each eye saw respectively only the remaining upper or lower part of the test line. The procedure in obtaining data as outlined above was then continued for a series of steps of decreased vertical gap, until finally stereoscopic depth could no longer be experienced.

The positions of the reference and test lines were interchanged, so that the reference line was then to the right, and the test line to the left, of the fixation point, and the entire experiment was repeated.

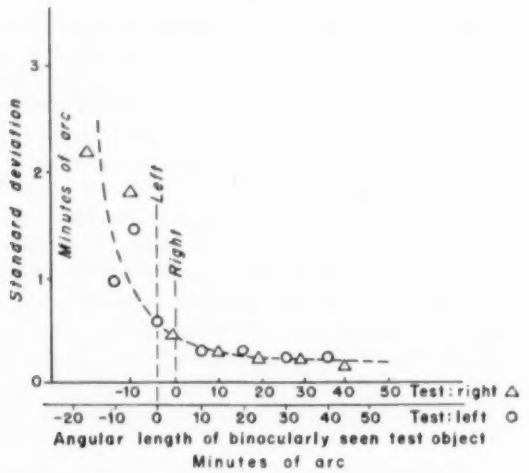

Fig. 2.—Change in the accuracy of stereoscopic vision, shown by standard deviations of settings, as the angular length of the portion of the test line seen binocularly is decreased. The settings were relative to the frontoparallel plane. Peripheral angle = 1.5 arc degrees. Reference and test lines exposed for only 0.2 second.

From the beginning of the experiment both subjects found the settings relatively easy to make as long as some portion of the test line was visible to the two eyes. When the gap closed, however, the judgments were more uncertain. Considerable change in disparity was necessary, and then no specific sense of a depth interval was experienced, but only a sense of "nearer" or "farther." If the baffle plates were set so that there was an actual separation between the half-images the judgments became still more uncertain. For larger separations even the sense of "nearer" or "farther" was lost.

An illustration of the quantitative results obtained by one observer is shown in Figure 2. The standard deviations of the settings are plotted as ordinates, and the angular lengths of the binocularly seen portion (the gap) of the test line are plotted on the axis of the abscissae. The two sets of data have been registered by a

shift in the two abscissal scales. Inspection of this graph shows a regular but small increase in the standard deviation as the binocularly seen portion of the half-images decreased. When the binocularly seen portion was reduced to zero and when the baffles were later adjusted so that there was an actual vertical separation between the half-images of the test line, the standard deviations increased markedly and were less consistent. Furthermore, in this negative gap range, no stereoscopic depth would be experienced for a large proportion of the times that the lines were exposed, and the observations were often uncertain and judgments difficult to make. The data do show that the steroscopic sensitivity is markedly decreased, or almost absent, when the gap has been eliminated.

A possible factor is present in the procedure just described when the disparity between the images of the test line is not zero, because the observer could not fail to be aware of the lateral (nonius or vernier) displacement of the two half-images with respect to each other. However, in spite of this empirical factor, there was a small subjective impression of depth even when there was a small but actual vertical separation between the two half-images. This result would be in agreement with those reported by van der Meulen and van Dooremaal, but the stereoscopic experience was certainly much vaguer than that suggested by these authors, and is certainly limited. Indeed, the data themselves show a low precision of an entirely different order than when some portion of the test object was seen binocularly. But even this vague sense of depth ceased when the half-images were separated very far. Thus, of greatest importance is the fact that even in this experimental arrangement there are definite limits in the amount of vertical separation of the half-images permissible if a depth impression is to be experienced.

Now we might anticipate that, in analogy with the vertical extent of Panum's areas of fusion, there could also be a vertical extent in areas for stereoscopic vision. That is, disparate images could also be vertically disparate, within certain limits, and still their horizontal disparity would be experienced in stereoscopic depth.‡ The existence of such areas was suggested by the experimental work on the induced effect.[13] The fact that a depth was experienced in the present experiments even after the half-images were slightly separated vertically might be explained on the basis that the inner ends of the two half-images fell within the vertical extent of these areas. Perhaps unsynchronized vertical nystagmoid movements and cyclotorsional movements of the two eyes would increase the apparent sizes of these stereoscopic areas. In Figure 2 one sees that the standard deviations become very large when the average separation between the half-images is about 16 minutes of arc. This might be interpreted, then, to represent the vertical extent of such areas. But this figure seems far too large in comparison with Panum's area to be correct.

We would conclude, then, that in the range of small horizontal disparities, for images near the central parts of the visual field, and for short exposures, in addition to the existence of such a retinal area of stereoscopic vision there appears to be some type of depth perception from vertically separated but horizontally disparate half-images. This result is in accordance with the experiment of van der Meulen and van Dooremaal. However, these authors do not report any limits in this depth experience.

‡ On the basis of his results with a particular instrument for testing depth perception, Loy [12] concluded that there was no such vertical extent.

The displacement of the two sets of data (test line to the left and to the right), which was not constant throughout the series of experiments, might be explained by (1) a cyclotorsional position of the eyes, (2) asymmetric properties of the retinas on the two sides of the foveas, (3) different irradiation effects from the baffle edges, and (4) errors in the baffle setting for zero gap. The last is probably the major source of the displacement.

II. *Reference Line in Frontoparallel Plane; Continuous Exposure of Reference and Test Lines.*—However, when the observations were made while the reference and test lines were continuously illuminated and therefore continuously visible, the apparent depth from the separated half-images was rarely experienced, or it was extremely variable and subjectively uncertain. With continuous visibility the stereoscopic sense of depth easily faded, and as the angle of disparity was increased, the depth became even less evident. That depth differences in general fade and finally

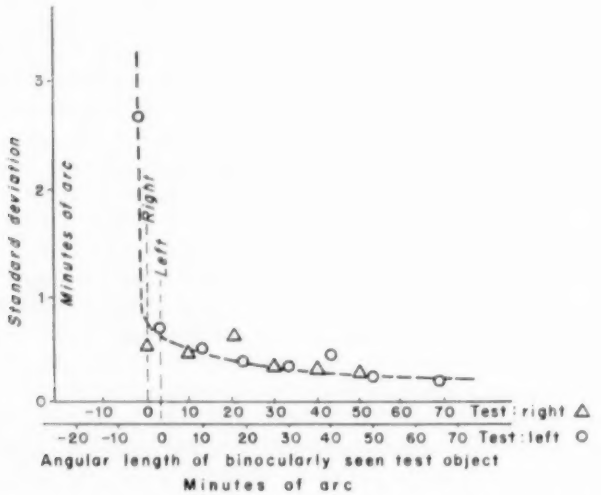

Fig. 3.—Change in the accuracy of stereoscopic vision, shown by standard deviations of settings, as the angular length of the portion of the test line seen binocularly is decreased. Settings relative to frontoparallel plane ($\eta_a = 0$). Peripheral angle = 1.5 arc degrees. Reference and test lines exposed continuously.

disappear with prolonged fixed staring is well known. Here, also, there was the annoying problem of suppression of one or both images. To restore the images, blinking of the eyes was constantly resorted to. There was, moreover, a compelling desire on the part of the subject to look away from the fixation point toward the test and reference lines. Data from which the standard deviations could be computed were much more difficult to obtain. The method of constant stimulus could not be used. Figure 3 illustrates data for one subject obtained with continuous illumination of reference and test lines. When the test line was to the right of the fixation point, no depth was experienced at all after the gap was closed.

III. *Reference Line in Frontoparallel Plane; Falling Sphere as Test Object.*—When the falling sphere replaced the test line, the experience of a depth was more

definite, and somewhat larger actual vertical separations between the half-images of the fall were possible. But although the percept of apparent "nearer" or "farther" than the fixation plane was present with the separated half-images, it was not experienced every time the sphere fell. The frequency with which the depth was not perceived increased as the separation of the half-images was increased. Thus, it appears that with the falling sphere a conception of depth based on disparity of separated images was possible for larger vertical separations of the half-images, but there was at the same time some indefiniteness regarding the depth. One must account for the somewhat increased perceptibility, with the falling sphere, by the shortness of exposure. Yet there are definite limits to which the half-images can be separated beyond which no conception of depth may be experienced.

IV. *Reference and Test Lines Seen in Front of (or Behind) Fixation Point; Short Exposures.*—The experimental set-up was then changed (1) to eliminate the empirical factor of the vernier displacement of the two half-images, (2) to test the possibility that the depth experienced from vertically separated half-images was a function only of small horizontal disparities, and (3) to test the possibility that the depth experienced from vertically separated half-images would not be proportional to the horizontal disparity. The reference line was placed at a given peripheral angle in front of (or behind) the plane of the fixation point corresponding to a given fixed disparity, for example, 1.5 cm. In the experiment the task of the subject was to adjust the test object so that it appeared at the same depth as the reference line, while fixation was still maintained on the original fixation spot. Thus, the images of both the reference and the test lines would be seen in approximately equal crossed (or uncrossed) disparity.

Certainly in the experimental procedure just described the lateral displacement between the upper and the lower half of the image caused by the horizontal disparity was an annoying factor that could not but interfere with the judgment of depth. The path of the falling sphere appeared to jump laterally at the gap. This jump tended also to influence the adjustment on the basis of apparent depth only. In the second arrangement, when the reference and test lines are to appear equally in front of (or behind) the fixation point, there must be a disparity, and therefore a lateral displacement, of the half-images.§ The possibility of memorizing the magnitude of the displacement is improbable.

Again, the depth perceived with slightly vertically separated half-images might occur only with relatively small horizontal disparities of the images or for objects in the neighborhood of the frontoparallel plane; that is, the concept or depth from the vertically separated half-images might be more evident relative to objects in the frontoparallel plane. The images might always give a depth experience of being farther or nearer than the fixation point, but a given horizontal disparity between the images might not be perceived as a specific depth interval from the plane of the fixation point.[9] This change in the experimental set-up would provide data on the quantitative aspect of horizontally disparate images which are vertically separated.

Figure 4 illustrates a set of data obtained for the reference and test lines placed at peripheral angles of 5 degrees ($\alpha_0 = 5$) on each side of the median plane. The

§ Within the areas of fusion the portion of the test line seen binocularly generally appeared in the same direction as the half-image seen by the dominant eye.[13]

reference line was placed about 1.5 cm. in front of the fixation point, a distance corresponding to a crossed disparity of the images (η_0) of about 13 minutes of arc. Again, the exposure time of both reference and test lines was 0.2 second. In the plotting of the data, little or no shift was necessary in the abscissa to register the two sets of data obtained when the test line was first on the left and then on the right side of the fixation point. In this graph the angular image disparity corresponding to the mean of the settings has also been plotted, as well as the standard deviations of the settings.

The following points should be noted from these data:

1. The standard deviation, as a measure of the stereoscopic threshold, now suddenly increased as the portion of the disparate half-images seen by the two eyes

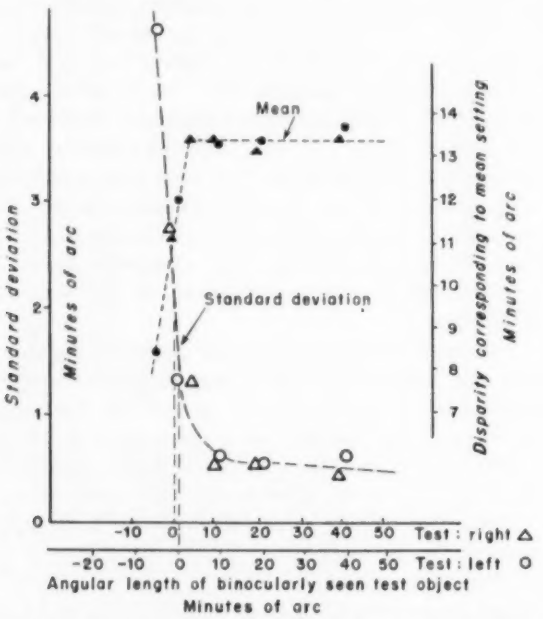

Fig. 4.—Change in the accuracy of stereoscopic vision, shown by standard deviations of settings, as the angular length of the portion of the test line seen binocularly is decreased. Settings made relative to a reference line seen in front of frontoparallel plane with a crossed disparity of 13.5 minutes of arc. Peripheral angle = 5 arc degrees. Reference and test lines exposed for only 0.2 second. Also shown are the disparities corresponding to the mean settings.

was decreased to zero. Thus stereoscopic depth virtually ceased when no portions of the horizontally disparate half-images could be seen binocularly.

2. When also plotted against gap length, the average disparity corresponding to the mean settings of both sets of data was fairly constant until the vertical gap between the baffles approached zero. Then the mean disparity for this subject, corresponding to apparent equal depth, suddenly decreased. This is to say that the depth of the test line as referred to that of the reference line was unchanged by a decrease in the length of the binocularly seen part of the test line, until it became

very small. Then the mean disparity between the half-images abruptly decreased. Now, a decreased disparity means that the test line would actually be placed nearer the fixation point than the reference line, though it appeared to be at the same distance. This behavior must be attributed to a loss of patent stereoscopic depth and the intrusion of empirical visual localization factors. Apparent distances of the reference and test lines are possibly being equated on the basis of apparent brightness, equality of length, or some similar factor associated with these lines. This change in the mean disparity was fairly consistent for most of the data taken by the one observer (K. N. O.), although occasionally in a given set of data it did not occur. For the other observer (R. H.), however, the break was more likely to be in the opposite direction; that is, the disparities of the images of the test line had to be

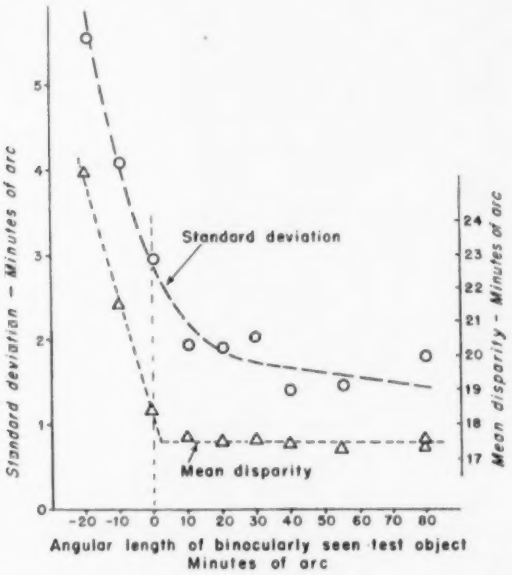

Fig. 5.—Change in the accuracy of stereoscopic vision, shown by standard deviations of settings, and the change in the mean disparity, as the angular length of the portion of the path traversed by a falling sphere (Hering) seen binocularly is decreased. Method of constant stimuli. Judgment of the fall made relative to a reference line seen in front of the frontoparallel plane with a crossed disparity of 17.5 minutes of arc. Peripheral angle = 1 arc degree.

increased (Fig. 5) in order for the test images to appear at the same distance as the reference line. That empirical factors are involved is suggested, because when the brightnesses of the reference and test lines were made very unequal, the direction of the change in disparity for the mean settings could sometimes be altered. The break in the line that describes the course of the mean disparities may be more important than the change in standard deviations in showing the breakdown of a patent stereopsis when simultaneous binocular perception is prevented.

We have evidence from these data, then, that the experience of a specific stereoscopic depth requires the participation of horizontally associated disparate retinal

elements. The vertical extent of stereoscopic areas when the images are also horizontally disparate based on this type of measurement certainly does not appear to be large.

When the falling sphere replaced the line, and then as the binocularly seen portion of the fall was decreased by closing the gap between the baffles, it became increasingly difficult to make the adjustments that would cause the falling sphere to appear as near in front of the fixation point as was the reference line. Again, in many falls no judgment could be made at all—there was no specific depth perception. And yet the subject usually felt that he could judge whether or not the falling sphere was nearer or farther than the fixation point itself, until the separation of the half-images became large.

With continuous visibility of reference and test lines, equal depth interval judgments could not be made when no binocularly seen portion of the test line was visible. Suppression of one or both of the half-images was particularly difficult.

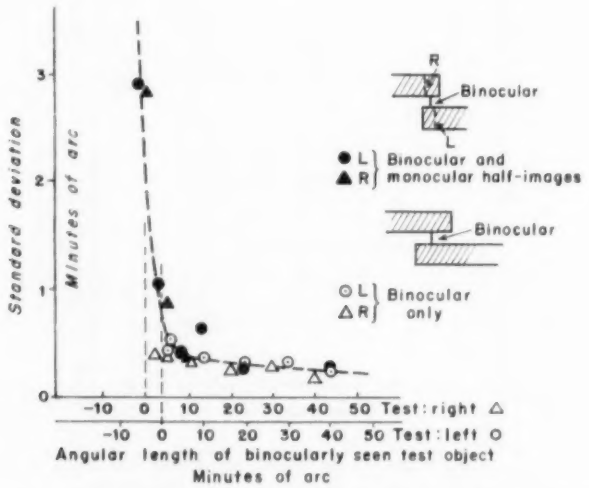

Fig. 6.—Change in the accuracy of stereoscopic vision, shown by standard deviations of settings, as the angular length of the portion of the test line seen binocularly is decreased, for two conditions: (1) with binocularly and monocularly seen half-images and (2) with only binocularly seen images of the test line. Settings of test line made relative to a reference line seen in front of the frontoparallel plane for a crossed disparity of 13 minutes of arc. Peripheral angle = 1.5 arc degrees. Reference and test lines exposed only 0.2 second.

V. Comparison of Data Obtained When the Entire Half-Images Were Visible and Those Obtained When the Only Images Seen Were Those Seen Binocularly.—It follows from the data illustrated in Figure 6 that the monocularly seen portions of the half-images do not contribute to the stereoscopic sensitivity provided by the binocularly seen portion of the test line. Two sets of data are shown on this graph. For the one set, the baffles were adjusted as they have been for all the previously described data, in that there was a binocularly seen portion and a monocularly seen portion. For the other set of data, the baffles were adjusted also horizontally so that the central portion of the test line only could be seen by the two eyes; that is, no part of the lines was seen monocularly. A decrease in stereoscopic sensitivity

might be expected as the length of the visible portion of the test lines was decreased, especially since the reference line was seen in a crossed disparity of 13 minutes of arc. The trend in the data is consistent with other data on stereoscopic acuity in similar types of experiments ‖ in which a fixed horizontal disparity was not involved.

An inspection of these two sets of data suggests that not only do the monocularly seen half-images not contribute to the stereoscopic sensitivity, but they may detract from it. The two sets of data obtained by the second observer showed less similarity.

COMMENT

The data, obtained by two subjects in the experiments just described, clearly suggest that there may be two aspects of stereoscopic depth perception: a quantitative, patent, or obligatory sense of depth, and a qualitative, or facultative perception of depth, both arising by virtue of disparity between the images. These two aspects of depth are probably the same as the "patent" stereopsis and "qualitative" conception of depth suggested by the experiments previously described on the disparity limits of stereoscopic vision.¶

As the term "obligatory" stereopsis implies, such depth perception is precise and subjectively certain. Subjective depth is related quantitatively to the disparity between the images in the two eyes. This type of stereopsis requires that there be simultaneous binocular perception in the sense that horizontally associated disparate retinal elements of the two eyes must be stimulated at the same time. This fact suggests that the basis of steroscopic depth perception must first be physiologic and be related to the neuroanatomic organization of the two retinas with the cortex.

The facultative depth perception need not be simultaneously perceived on horizontally associated disparate retinal elements in the two eyes. This perception may be a visual comparison of distances of the half-images from the images of the fixation point. The perception is a somewhat vague experience of depth and seems to be more evident for objects near the objective frontoparallel plane and the point of fixation than for objects in other positions. The depth is much more uncertain when the images are continuously seen, rather than when briefly seen, and when no eye movements occur. Short exposure of details enhances this depth experience. In ordinary surroundings fixating eye movements from one object to another would accordingly enhance this facultative experience of depth. An increased number of objects in the field of view with the accompanying increase in binocular parallax clues would also enhance this facultative aspect of depth experience. We would be led to believe that the facultative depth perception is empirical, based on parallax clues, and results from experience in the life of the individual.

The results of the experiment of van der Meulen and van Dooremaal would probably be explained on the basis of this facultative depth perception. That the conclusions of these authors pertain to all of stereoscopic depth perception must be rejected.

If we assume these two phases or aspects of stereoscopic depth perception as outlined above, we may understand certain other known phenomena of spatial localization. Persons who have differences in magnification between the images of the two eyes (aniseikonia) or in whom these differences are introduced by afocal

‖ References 14 and 15.

¶ References 10 and 11.

magnifying lenses # seldom report disturbances in spatial localization after a few days, except in surroundings where stereoscopic vision is forced because of a paucity of empirical clues. We could assume that in familiar surroundings the obligatory stereopsis in these persons is suppressed over the entire visual field. This suppression still permits the facultative depth perception to assist in "farther" and "nearer" discrimination without there being the false spatial localization associated with the quantitative influence of the differences in image magnification on the disparities between the images.

Again, there are persons who, in spite of normal fusion and normal visual acuity in each eye, still have poor stereoscopic depth perception. Here we may also assume that the physiologic obligatory stereopsis has never fully developed or is deeply suppressed. The facultative depth would, nevertheless, be present. Training procedures to improve stereopsis in these persons cannot be very successful.* The facultative perception of depth might, on the other hand, be improved to some extent with training.

SUMMARY

Data are described which suggest that there are two aspects of stereoscopic depth perception: (1) a true quantitative, or obligatory, sense of depth that necessitates the simultaneous stimulation of horizontally associated disparate retinal elements, and (2) a vaguer qualitative, or facultative, percept of depth, also arising from disparate images. This provides the individual with an experience only of "farther" or "nearer" than the point of fixation; this perception appears to be empirical in nature. The obligatory, or true, stereopsis, because of the limitation imposed through the necessity of stimuli falling on horizontally associated disparate retinal points, implies a physiologic and neuroanatomic basis.

The facultative depth perception would be classed with the empirical factors of spatial localization.

The experiments show that the facultative depth is enhanced by momentary stimuli, but depressed with continuously visible disparate stimuli. Eye movements would enhance this aspect of depth perception.

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ELECTROMYOGRAM OF THE EXTRAOCULAR MUSCLES OF THE RABBIT IN SITU

Evidence Confirming Its Source

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IN THE course of efforts to obtain a recording method for measuring objective thresholds of vestibular stimulation, the possibility of using muscle action potentials directly from the extraocular muscles was explored.

HISTORICAL REVIEW

Bartels [1] in 1911 published work on a method of recording the mechanical action of the extraocular muscles. The animal was placed on a rotary platform with the recording apparatus, and, with use of levers, movements of the extraocular muscles were recorded directly.

Hoffmann in 1913 [2] modified the apparatus of Bartels and recorded action potentials from the extraocular muscles, likewise directly.

Köllner and Hoffmann in 1921 [3] recorded action potentials from the extraocular muscles of the rabbit and studied the relationship of the nystagmus to ear functions.

Perez-Cirera in 1932,* using a more refined apparatus than Köllner and Hoffmann, made more accurate records of the action potentials of the extraocular muscles than had previously been reported.

Lorente de Nó in 1935,[5] while investigating the synaptic delay of the motoneurons, used a preparation and apparatus that gave excellent records of action potentials from the extraocular muscles. The responses were not reflex or voluntary but were artificially induced by a stimulator.

Brown and Harvey in 1941 [6] studied neuromuscular transmission in the extraocular muscles of the cat. Here they used artificial stimulation with electric shocks and certain drugs, such as physostigmine, in the blood stream to produce a type of release contraction, and they recorded the results with both agents.

Reid in 1949 [7] obtained action potentials from the extraocular muscles in animals, using reflex movements of the head as a stimulus for the twitch.

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Dr. Harry Grundfest gave the use of valuable equipment, and Dr. William Rogers and Dr. V. N. Epanchin assisted in the experiments. Dr. Philip Knapp and Dr. A. C. Hilding introduced the electrodes into the author's eyes.

Pulfrich in 1952 [8] improved the method of Perez-Cirera and obtained records of action potentials from the rabbit during nystagmus. This investigator removed the eyeball in the preparation of the animal.

Adler in 1953 [9] published work on action potentials from the extraocular muscles of the human. The records were obtained during studies of divergence.

Further studies were made on mechanical methods of recording actions of the extraocular muscles by McCouch and Adler,[10] Lorente de Nó (1933),[11] and de Kleyn,[12] as well as others.

In 1922 Schott [13] published work on the so-called corneoretinal potentials, and there have been many investigators since: Meyers [14]; Mowrer, Ruch, and Miller [15]; Fenn and Hursh [16]; Jung [17]; Lindsley and Hunter,[18] and Perlman and Case,[19] with more recent publications by Glorig and Fowler [20] and Montandon and Monnier.[21] This work is mentioned because for a while these corneoretinal potentials were thought to be action potentials from the extraocular muscles.

An historical review of the subject of action potentials from the extraocular muscles reveals that confusion existed for a while because of lack of understanding of the principles involved.

It is well to point out in the beginning of any discussion on action potentials of the extraocular muscles that these potentials are only part of a group of electrical potentials associated with the visual apparatus.

TYPES OF ELECTRICAL POTENTIALS ASSOCIATED WITH THE VISUAL APPARATUS

There are several types of electrical potentials to be considered when studying the visual apparatus. First of all, there is the corneoretinal potential group, the situation wherein the posterior part of the globe is negatively charged and the anterior part positively. If electrodes are placed on the orbital margins, this potential is seen to vary with rotation of the globe. Second, there are the electrical potentials of the various nerve structures of the visual apparatus. Among these are the potentials in the electroretinogram and action potentials from the various nerves (McIntyre, 1939 [22]). The electrical potentials of the visual cortex are recorded in the electroencephalogram (Callahan and Redlich, 1946 [23]). Third, there are the action potentials associated with muscular structures of the visual apparatus. These are of various types, depending on the location of the electrodes. They may arise from a single muscle or from a group of muscles. Sources of such action potentials are the extraocular muscles, the levator, the orbicularis, and other muscles about the orbit. Furthermore, if one electrode is placed on an ocular structure and the other active electrode is placed at some distance (e. g., the hind paw in the animal), it is possible that electrical potentials can be picked up from body structures, such as the heart. Not much information is available concerning the electrical activity of the ciliary muscle or iris (Young, 1944 [24]).

With such a number of electrical potentials associated with the visual apparatus, it is obvious that methods must be used whereby a potential from a known source can be identified for purposes of study. It is obvious, also, that in discussing the potentials of the extraocular muscles, including the four recti, the two oblique muscles, and the levator only, we must consider only potentials from each of these muscles, and from no place else.

With these points in mind, a method was sought for obtaining action potentials from the extraocular muscles directly and, what is more important, with minimum disturbance to the normal anatomical features of the field involved.

METHOD

A high-gain preamplifier and a cathode ray oscilloscope (Dumont Model 322) were used for these studies. The action potentials were visualized on the tube face and photographed with a continuous-motion camera.* The X-axis of the oscilloscope was turned off; calibrations are given on the records. For more details about the preamplifier, the article by Yahr and associates[25] may be consulted.

A box with a small opening for the head was best suited for restraint of the animal. Simple aseptic technique was used and an antibiotic powder applied after the procedure. The experiments were done with local 2% tetracaine surface anesthesia. Electrodes were of 40-gauge enamel-covered copper wire.

The conjunctiva and Tenon's capsule were dissected from the surface of the medial rectus muscle and the sclera on both sides dissected free of episcleral tissue. The copper wire was denuded (chemically)† for a distance of about 2 mm. at a known distance from the end, washed off with water, and threaded on a small curved or straight needle. One bite was then taken in the sclera on one side of the muscle; then a bite in the muscle belly (about 5 mm.), and then another bite in the sclera on the side opposite the first. The electrode was then adjusted so that the denuded portion could be seen in the muscle belly (the bite was such that the electrode was visible in the muscle tissue), and then the electrode was bent on the outside of each scleral bite so that there was practically no movement of the wire. The short end was taped to the proximal end and the lead connected to the preamplifier. Two such electrodes were placed about 6 mm. apart: The one farthest from the cornea was connected to the active input, and the one nearest the cornea, to the indifferent lead. A ground of rolled tin, about 1 in. (2.5 cm.) square, was placed on the ear. Electrode jelly was used on the skin of the ear under the electrode. Solder was used to reinforce the connections of the electrodes to the leads. The three leads were taped to a segment of tongue depressor blade, which, in turn, was taped to the surface of the head of the animal or to the box, close to the head.

A modification of the above technique was used with equal success on a human subject (myself).

Retrobulbar injection of procaine hydrochloride of various strengths was given (1 cc. of a 5% solution was found best); records were made before and after retrobulbar injection to show the effect. Rotation nystagmus‡ was used to prove the effect of the retrobulbar injection. The animal was rotated clockwise and counterclockwise through 180 degrees on a small rotary platform to produce the nystagmus.

Nine eyes were studied in this experiment.

RESULTS

Record with Both Leads Grounded.—Figure 1 shows the record obtained with both leads grounded. Here the ground, input, and indifferent leads are in contact, demonstrating minimal interference. The fine irregularities on the upper and lower borders of the isoelectric line are referred to as "noise" of the preamplifier and the oscilloscope. With this particular combination of machines, the noise level is about 3 μv.§

Record from the Medial Rectus at Rest.—Figure 2*a* is the record from the medial rectus with the animal at rest. The eye does not move grossly. The isoelectric

* The camera is manufactured by the Grass Instrument Company. A special device for attachment to the camera was developed by Dr. V. N. Epanchin; this enabled rapid labeling of the record—a very important consideration.

† A commercial solvent called Strip-X was used, marketed by General Cement Manufacturing Co., Rockford, Ill.

‡ Since the animal's eyes were open, the nystagmus was not purely of the rotation type.

§ At the higher gains interference from the camera was noted in the form of increased amplitude of the noise.

line is irregularly wavy, and there is evidence of electrical activity in the appearance of spike potentials. These are of low amplitude and variable frequency. Potentials are about 4 msec. in duration and vary in amplitude. The amplitude of the potential is probably related to the position of the electrodes with respect to the motor units firing and the relation of the electrodes to each other. Frequency is probably related to the amount of muscle activity. The record varies constantly.

Record After Retrobulbar Injection of Procaine.—Figure 3*a* shows the record from the same preparation as that in Figure 2*a* after retrobulbar injection of procaine. The record appears as in Figure 1. Figures 4 and 5*a* (same preparation as

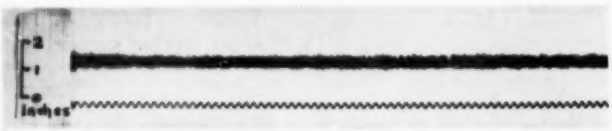

Fig. 1.—Record obtained with the ground and leads in contact. The amplitude is 16 μv per inch; the time signal, 50 cps, and the speed of the paper, 100 mm. per second. Paper speed is 100 mm. per second unless noted otherwise.

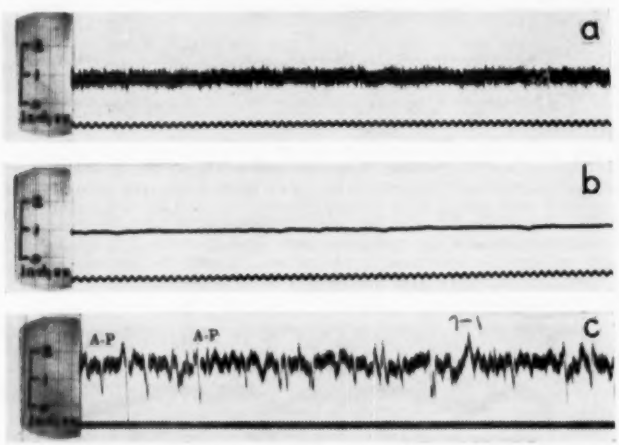

Fig. 2.—(*a*) Record from the medial rectus of the rabbit with the animal at rest in a box. Calibrations as in Figure 1. This and all succeeding records are with the animal in the box as described in the text. Likewise, all succeeding records are read from right to left.

(*b*) Record similar to *a* except that the gain has been reduced 10 times, so that the amplitude is 160 μv per inch. It is apparent that the record with low gain is not as informative; however, it is not possible to use the high gain during rotation nystagmus, for the record then goes off the film.

(*c*) Record similar to *a*, but from a different preparation. The amplitude is 16 μv per inch; the time signal, 250 cps, and the paper speed, 250 mm. per second. Spikes are more obvious, the reason, in all probability, being the position of the electrodes. Action potentials are marked *A-P*.

that in Figure 2*a*) show the response from the medial rectus during rotation before and after retrobulbar injection respectively. The absence of response is obvious in Figure 5. (Figure 4 is comparable to the records of Pulfrich,[8] though different types of electrodes and calibrations are used.)

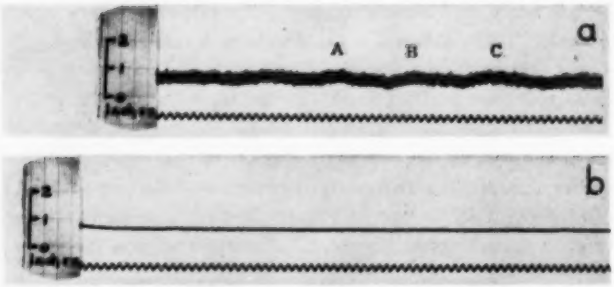

Fig. 3.—(*a*) Record from the right medial rectus two minutes after a retrobulbar injection of 1 cc. of 5% procaine hydrochloride. Amplitude is 16 μv per inch and the time signal 50 cps. The animal is at rest. Note that Figures 1 and 3*a* are fairly comparable: The difference between Figure 2*a* and Figure 3*a* is apparent. (Figures 2*a* and 3*a* are from the same preparation.) *A*, *B*, and *C* are variations in the isoelectric line, probably due to some movement in the preparation.

(*b*) Record similar to *a*, but the amplitude is 160 μv per inch. It can be seen that with a low amplitude, important details are lost, for Figure 2*b* and Figure 3*b* are similar except for a slight waviness in Figure 2*b*, whereas a difference is obvious in Figure 2*a* and Figure 3*a*, where the gain is increased tenfold.

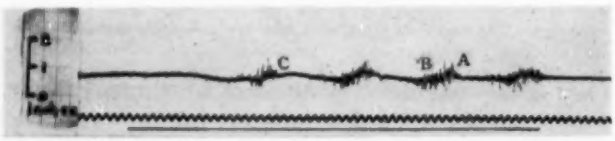

Fig. 4.—Record from the right medial rectus of the rabbit during counterclockwise rotation before retrobulbar injection of procaine. The amplitude is 160 μv per inch and the time signal 50 cps. Below the time signal the beginning of the black mark represents the beginning of rotation; however, the method used in indicating the beginning of rotation did not permit an approximation closer than 1/10 second; this holds true for the records following with rotation. *A* marks the beginning of the quick phase of the nystagmus jerk, and *B*, the end. *C* represents the period of little or no activity before contraction. A similar record with the amplitude at 16 μv per inch is not satisfactory, for the record goes off the film for a large part.

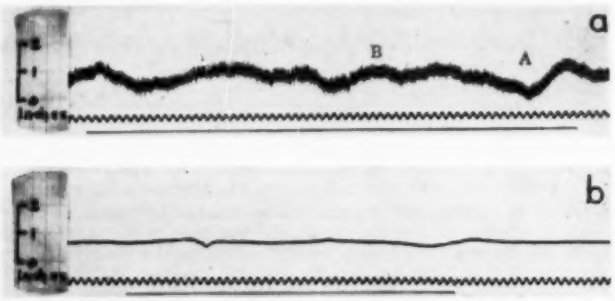

Fig. 5.—(*a*) Same preparation as that in Figure 4, with the record taken a few seconds later. Amplitude is 16 μv per inch and the time signal 50 cps. There is noted a minimal amount of activity after the counterclockwise rotation; the cause of this is not obvious. It will be remembered that a similar record before retrobulbar injection was not obtained because it went off the film, the response being so large. *A* and *B* are probably due to movement somewhere in the preparation, incidental to rotation.

(*b*) Record shown for purposes of comparison with Figure 4. It is the same as Figure 5*a* except that the gain has been reduced 10 times, to 160 μv per inch, thereby permitting the whole record on the film.

COMMENT

The significance of the record with both leads grounded is that it is the basic element, and anything added to this represents activity from one or more sources. It is important to know the source of additions to the basic isoelectric line, for only then can we interpret the complex record patterns obtained.

Blockage of nerve trunk conduction, and probably myoneural junction conduction, is the effect produced by the retrobulbar injection, for this is the action of procaine. Mechanical intraorbital pressure is probably not a factor. The site of action of the procaine is presumably on the nerve trunk for the most part. The effect on the myoneural junction probably depends on its location in the orbit. Afferent and efferent impulses traveling in the cranial nerves in the orbit, as well as other intraorbital nerve tissues, are affected by the retrobulbar injection.‖ Mechanical myograms from the extraocular muscles [1] indicate that the principal factor in producing nystagmus is the action of the extraocular muscles. Retrobulbar injection of procaine stops nystagmus grossly on the side of injection in rabbits. From experience in the operating room it is known that one of the principal effects of the retrobulbar injection in the human is blockage of efferent third and sixth nerve motor impulses. It would seem that the effect of the retrobulbar injection of procaine on the electromyogram of the medial rectus muscle in the rabbit is probably due mostly to blockage of third nerve efferent motor impulses. The corollary to this is obvious. Blockage of other types of nerve impulses might conceivably have an effect also.

Recordings from the medial rectus of the rabbit at rest can be regarded as the basic isoelectric line with certain elements added. These elements are a type of activity characterized by spikes of low amplitude and varying frequency. In addition, the record is irregularly wavy. By a retrobulbar injection of procaine the composite nature of the resting electromyogram can be shown, for it is possible to eliminate the spike potentials and the waviness and produce the picture of the circuit with both leads grounded.

It is well to point out here that the area for picking up action potentials from the medial rectus muscle in the rabbit is not limited to the tendon and belly of the muscle. The pick-up area (we might say, the electrometric pick-up field extends for a distance away from the muscle itself. The delineation of the electromotor pick-up field for each muscle is a study in itself; the effect of the retractor bulbi is also a factor to be considered in the rabbit.

The relationship of other action potentials associated with the visual apparatus to the electromyogram of the extraocular muscles is of great importance. The so-called corneoretinal potentials are of much greater amplitude than the potentials of the electromyogram of the extraocular muscles; furthermore, the former require orbital electrodes. The fact that the retrobulbar injection can eliminate practically all features of the electromyogram except the basic element indicates that we are not dealing with the electrocardiogram or other such impulses. It is obvious that the electrocardiogram would persist after a retrobulbar injection of procaine. The same that is said of the electrocardiogram may be said for overflow from facial or neck muscles. These impulses would not be eliminated by a retrobulbar injection of

‖ The exact effect of retrobulbar injection of procaine on the second cranial nerve is not clearly described in the literature.

procaine if they were producing the effect found in the electromyogram of the extraocular muscles. The features added to the basic element to produce the electromyogram of the extraocular muscles are likewise not currents of injury, for such impulses would not be eliminated by a retrobulbar injection of procaine. Proprioceptive impulses are picked up from nerves themselves, and these with difficulty, so that it is doubtful whether such impulses are being recorded in the method described. Since the ciliary body and iris consist of smooth muscle, it is fairly certain that potentials from these muscle structures are so small that they do not affect the electromyogram of the extraocular muscles. Further study is required to see

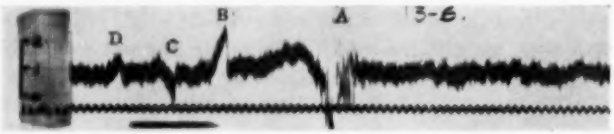

Fig. 6.—Record of blinking made with electrodes in the right medial rectus. The retrobulbar injection of 1 cc. of 5% procaine hydrochloride has taken effect. Amplitude is 16 μv per inch and the time signal 50 cps. Below the time signal there is a black mark representing the time the observer pressed the button to indicate the blink. *A* is the blink response; *B*, *C*, and *D* probably are movements of the electrodes. Included in *A* is a variation in the isoelectric line, also probably due to movement of the electrodes. The response most likely originates in the orbicularis oculi.

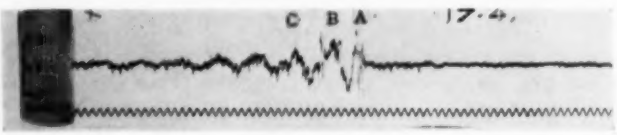

Fig. 7.—Record when the animal was made to move the head rather violently from side to side by irritating his nose with a piece of paper, indicated by the black line below the time signal. Electrodes are in the right medial rectus. Amplitude is 160 μv per inch and the time signal 50 cps. Wide variations in the isoelectric line are apparent at *A*, *B*, and *C*. Superimposed on these are potentials no doubt associated with movements of the globe.

Fig. 8.—Same preparation as that used in Figure 7 after a retrobulbar injection of 1 cc. of 5% procaine hydrochloride had taken effect. The only difference is the absence of small potentials; the changes in the isoelectric line are apparent.

whether there is a relationship between the electroretinogram and the electromyogram of the extraocular muscles. All the experiments were done in daylight with the animals' eyes open; no change in light was necessary for photography. There is evidence of some kind of activity, however small, in the records—during rotation only, after retrobulbar injection (Fig. 5). It is difficult to establish the cause of this phenomenon; movements associated with rotation, movement of the electrodes, etc., are possibilities.

So far, two types of activity can be recognized in the electromyogram of the extraocular muscles, the origin of which is not electrical activity of the extraocular

muscles. First, activity of the orbicularis oculi muscle is manifest with each blink of the lids, even after retrobulbar injection of procaine (Fig. 6). Second, variations in the isoelectric line (without potentials) are evident after retrobulbar injection of procaine on strong movements of the head (Figs. 7 and 8). These variations in the isoelectric line are possibly due to movements of a particular part of the preparation.

SUMMARY

1. A brief historical review of action potentials from the extraocular muscles is given.

2. Experimental techniques are described and results shown.

3. The electromyogram from the medial rectus of the rabbit is shown at rest.

4. Some evidence is offered confirming the origin of the electromyogram of the medial rectus from that muscle.

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ELECTRORETINOGRAPHIC STUDIES IN ARTERIAL HYPERTENSION

Effect of Reduction in Blood Pressure on Electrical Response of Human Retina

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AND
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IN RECENT years the ophthalmologist has often been confronted with the problem of arterial hypertension, as in modern therapy ophthalmoscopy is of great importance in the prognosis of the disease.

It seems to us of interest to see whether, in addition to use of the ophthalmoscopic picture, visual acuity, and visual fields in judging the retinal function, a method can be developed by which a really objective judgment of the retinal function can be obtained.

As the electrocardiogram is closely related to the metabolic condition of the retina, electroretinography offers, in our opinion, such an objective method for the examination of retinal function. The relation between the electrical response and the retinal metabolism has been discussed extensively in previous papers.*

The present paper deals with the influence of reduction in blood pressure (both acute and of a longer duration) on the electrical responses of the human retina, whether this reduction is produced by conservative therapeutic measures (rest, diet, and sedatives) or by antihypertensive drugs (hexamethonium and alkavervir [Veriloid]). These two drugs have different actions: Hexamethonium has a ganglion-blocking action, whereas alkavervir acts centrally.

It seemed to be of interest to compare the actions of these drugs on the ERG in cases of hypertension.

The ocular effects of hexamethonium have been reported in detail, i. e., lowering of intraocular pressure (Barnett,[5] Pau [6]), and an effect on accommodation and pupillary reactions. As far as we know, the specific ocular effects of the alkaloids of Veratrum viride have not yet been reported.

MATERIAL

Electroretinographic studies were performed on 32 patients with arterial hypertension, all treated with hexamethonium and alkavervir. These patients showed various retinal pictures: (*a*) hypertensive retinopathy, Grade I or II, 10 cases; (*b*) hypertension retinopathy, Grade III or IV, 10 cases; (*c*) occlusion of central or retinal veins, 7 cases; (*d*) pseudoglaucoma, based on hypertensive sclerosis, 2 cases, and (*e*) normal fundi, 3 cases.

The electroretinographic control study was performed over a period of 1 to 15 months.

* References 1 through 4.

In all cases we studied the influence of an acute reduction in blood pressure caused by an intravenous injection of hexamethonium and of alkavervir, as well as the prolonged effect of these drugs, on the electrical response of the retina.

Both drugs were used only where conservative therapy (rest, adequate diet, and general therapeutic measures) had failed to produce an adequate fall in blood pressure.

A two-channel amplifier was used for the simultaneous recording of the ERG of the two eyes. The technique of recording was essentially the same as that previously described.

As one of us (H. E. H.) has shown before,[4] it is essential in clinical electroretinography to record the ERG not only after a preliminary rest and dark adaptation of 5 minutes, but also after 30 minutes of rest.

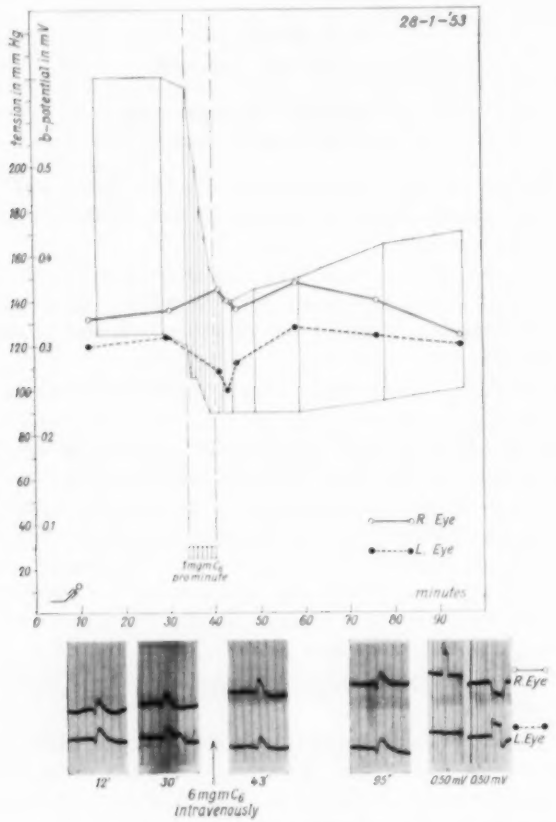

Fig. 1.—Curves representing the course of blood pressure and electrical response of the retina following an intravenous injection of hexamethonium.

In all patients test doses of hexamethonium and of alkavervir were given intravenously, with an interval of two days between the injections.

Electroretinography was performed with more or less continuous measurement of the blood pressure. A comparison of the effect of hexamethonium and that of alkavervir on blood pressure and electrical response was thus made possible.

The subsequent antihypertension therapy, using the two drugs under discussion, was based on the quantity, given by intravenous injection, necessary to obtain a sufficient decrease in blood pressure. A tension of 150/90 was aimed at.

RESULTS

A. Effect of Acute and Short-Lasting Reduction in Blood Pressure on Electrical Response of Retina.—In several patients treated with hexamethonium and alkavervir the lowering of the blood pressure gave rise to interesting observations. The following cases are worth reporting.

J. H., a woman aged 60, was suffering from hypertensive retinopathy, Grade III (Keith-Wagener), complicated by occlusion of one of the retinal veins in the right eye. After the

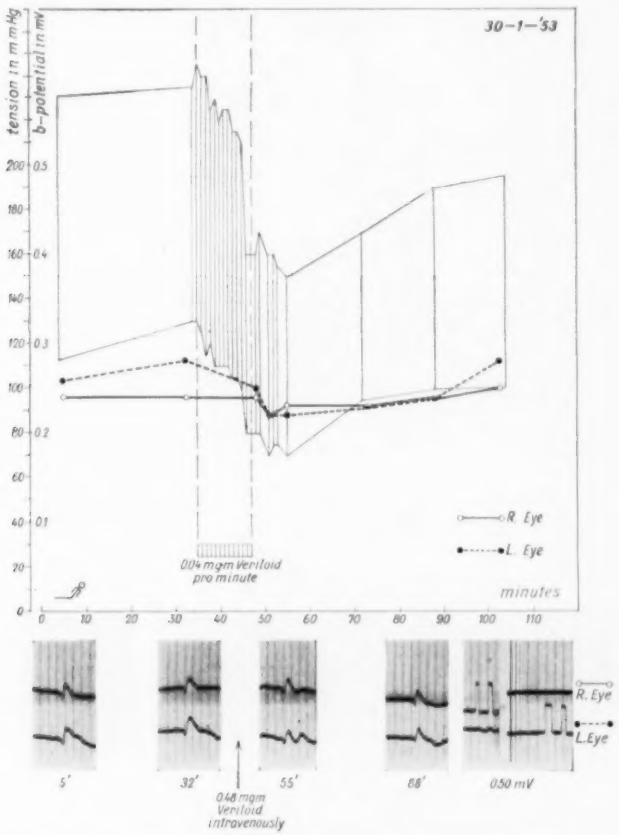

Fig. 2.—Effect of intravenous injection of alkavervir on blood pressure and electroretinogram in the patient referred to in Figure 1.

usual period of rest and dark adaptation of five minutes, both eyes showed a negative + ERG with a marked a-wave and a b-wave of normal height. No alteration in the electrical response was recordable after a prolonged rest in the dark of up to 30 minutes.

The marked a-wave points, in our opinion, to a disturbance in the retinal metabolism, not only of the diseased eye but also of the sound one.

After an intravenous injection of 6 mg. of hexamethonium, the blood pressure fell rather acutely from 240/125 to 140/90. However, we could not observe a significant decrease in the

b-potential following the injection (Fig. 1). Before the blood pressure regained its initial value, a normalization of the electrical response was observed.

An intravenous injection of 0.48 mg. of alkavervir given two days later showed a somewhat similar effect: an abrupt lowering of blood pressure without much change in the electrical response of the retina (Fig. 2).

As a result of the effect obtained by the injection of hexamethonium, treatment was started with subcutaneous injections of 6 mg. of hexamethonium, three times a day.

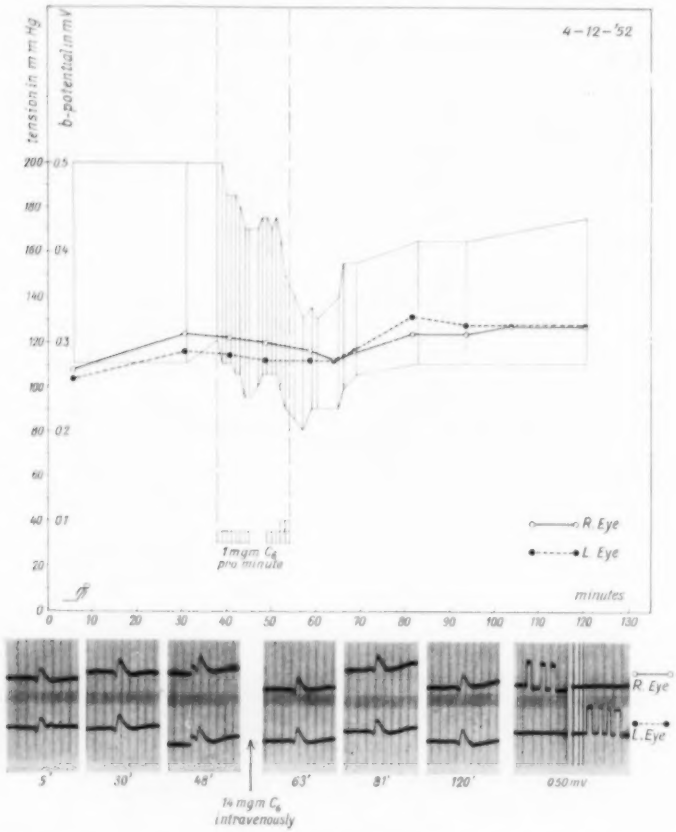

Fig. 3.—No essential alteration in the electrical response of the retinas with hexamethonium.

J. O., a woman 56 years of age, was suffering from hypertensive retinopathy, Grade III, with occlusion of retinal veins in both eyes. The ERG recorded after 5 minutes of rest in the dark room did not differ much from the records taken after 30 minutes of rest. The ERG was of the normal type, showing, however, a rather marked a-wave.

After the first intravenous injection of hexamethonium, the ERG showed very little alteration (Fig. 3).

Even the extreme reduction in blood pressure obtained after an intravenous injection of 0.80 mg. of alkavervir, producing a fall from 200/120 to 85/55 in a relatively short period, was unable to produce a significant decrease in the b-potential of the ERG (Fig. 4).

In this patient we have to accept that even a marked decrease in the minute volume of the heart seems to be of little importance in the maintenance of a normal electrical response of the retina. Whether such behavior may be regarded as a favorable sign in the prognosis of the retinal affection will be discussed in more detail in the following pages.

E. J., a woman aged 66. Diagnosis: Hypertensive sclerosis of retina and optic nerve. A marked constriction of the visual fields was present; the intraocular pressure, however, was

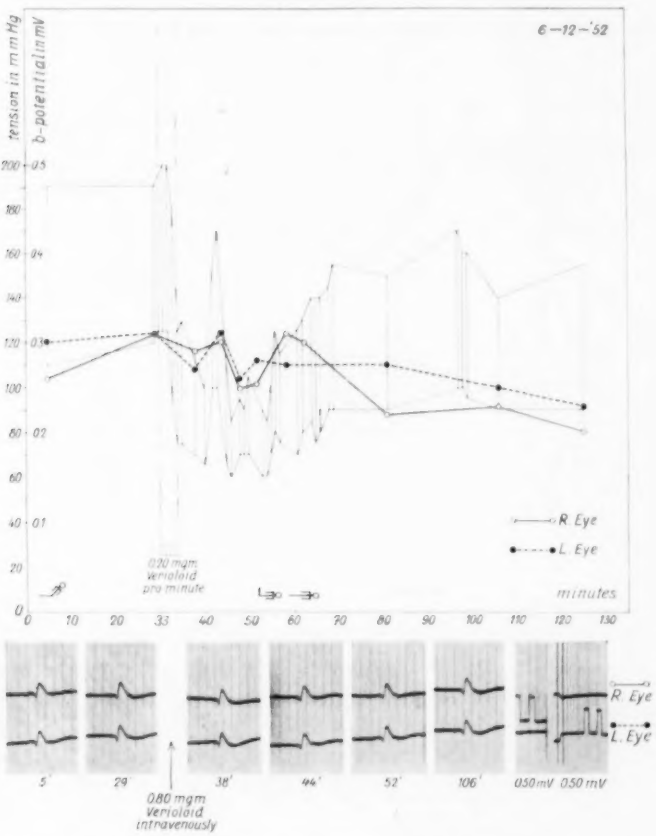

Fig. 4.—Only slight alteration in electrical response with even extreme variations in blood pressure following intravenous injection of alkavervir. Same patient as that referred to in Figure 3.

normal. A marked general arteriosclerosis, with hypertension of 220/110, was noted. After an intravenous injection of 5 mg. of hexamethonium, the blood pressure fell to 135/85. An immediate decrease in the b-potential of the ERG was observed (Fig. 5). The initial value was regained rather slowly as compared with that of the patients described above.

Two days later a test dose of alkavervir was administered intravenously. Previous to the injection a considerable gain in b-potential had been recorded after prolonged rest in the dark room of up to 30 minutes (Fig. 6).

During the fall in blood pressure, which was somewhat alarming, owing to the injection being made too quickly and the amount of alkavervir given being rather large, a considerable decrease in b-potential was observed. Yet before the blood pressure had been restored to a more or less stable level, the b-potential had already gained considerably in height.

We are inclined to believe that these alterations in the electrical responses of the retina following the decrease in blood pressure point to an insufficient retinal metabolism, at least when the general circulation is affected by lowering of the blood pressure. Whether such behavior may justify the acceptance of a poor prognosis of the

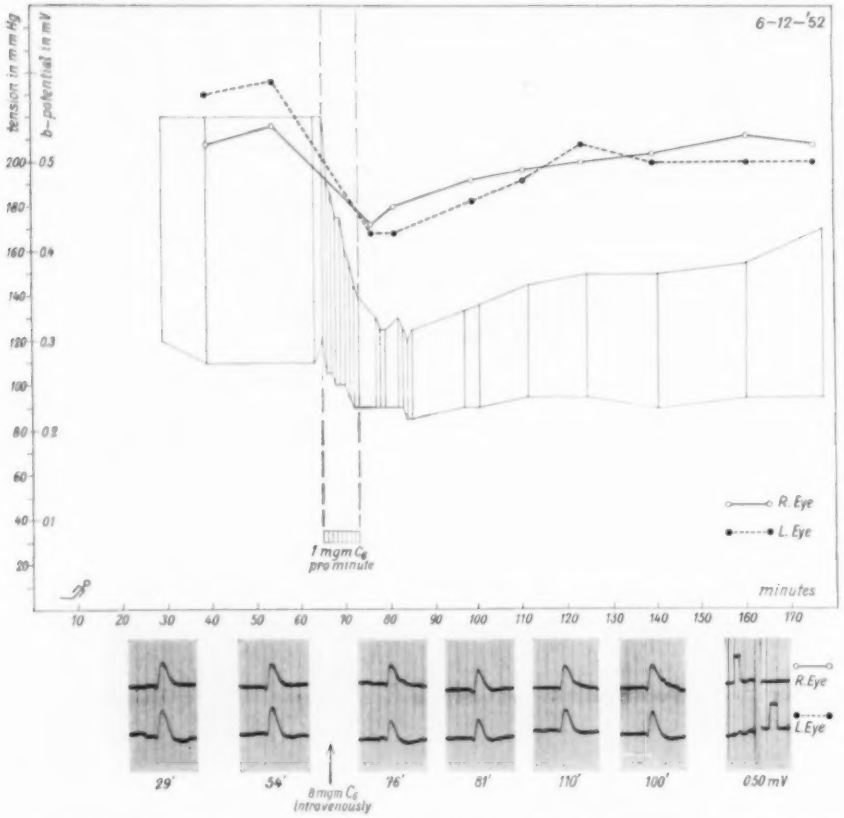

Fig. 5.—Significant decrease in b-potential following decrease in blood pressure after an intravenous injection of hexamethonium.

retinal process remains an open question, as at least in this case the reduction in blood pressure was considerably greater than the reduction to 150/90 aimed at.

The direct relation between blood pressure and electrical response is shown in more detail in the curves given in figure 7.

A. H., a man aged 58, suffered from hypertensive retinopathy, Grade II, of both eyes.

The blood pressure and electrical response were recorded continuously. At first, the fall in blood pressure was not followed by a decrease in the b-potential. Not before the blood

pressure registered as low as 70/45 could an acute decrease in height of the b-wave be recorded! The height of the b-potential showed an appreciable increase and a tendency to normalization when the blood pressure had regained a level of only 100/65!

Whether we may conclude from the recovery in the b-potential that a corresponding recovery occurred in the disturbed retinal metabolism will be discussed in the following pages.

B. Effect of Slow and Persistent Reduction in Blood Pressure on Electrical Response of Human Retina.—In several cases of hypertensive retinopathy without

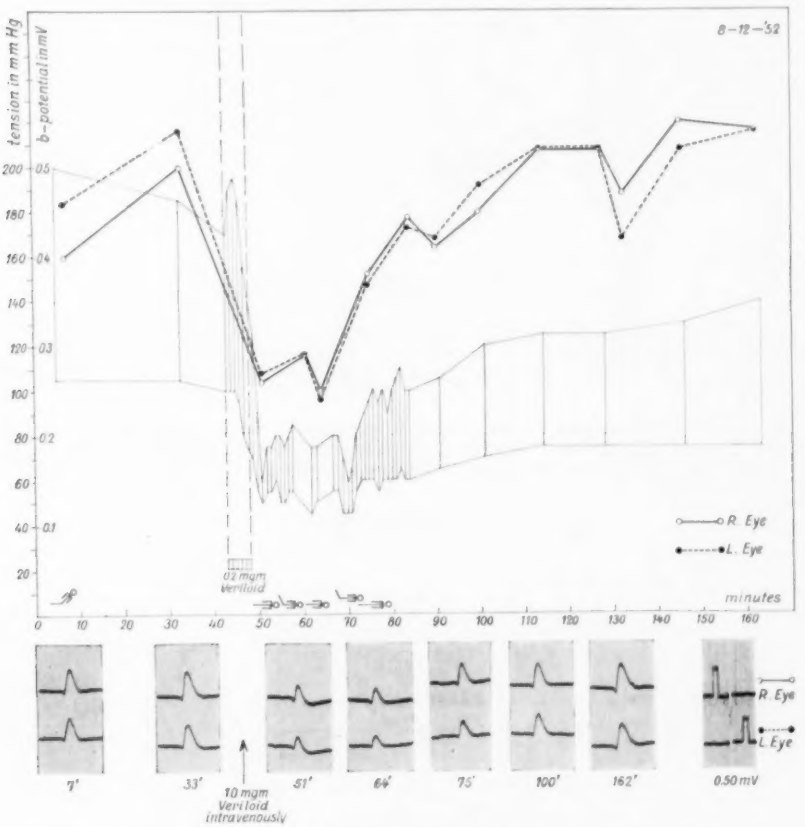

Fig. 6.—Alarming decrease in electrical response of the retinas resulting from intravenous injection of alkavervir, in the same patient as that referred to in Figure 5.

arteriosclerosis, a normalization in blood pressure was observed as a result of conservative therapeutic measures (rest, adequate diet, sedatives). The supernormal electrical response, recorded in most cases, tended to change to a response with a b-wave of normal height.

Figure 8 illustrates such a decrease in the b-potential in a patient suffering from hypertensive retinopathy, Grade III.

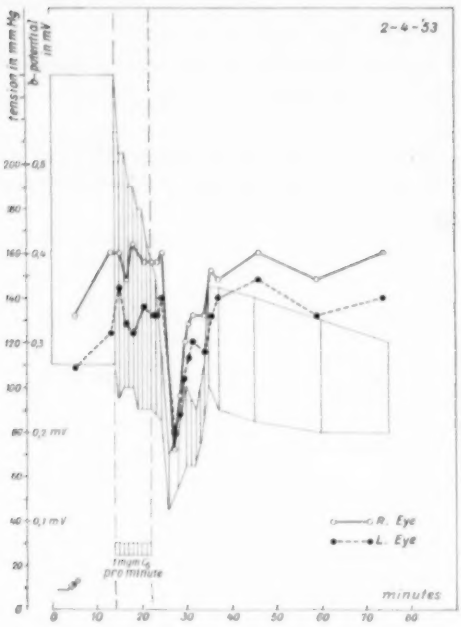

Fig. 7.—Curves representing the direct relation between the blood pressure and the electrical response of the retinas. At first, the fall in blood pressure is not followed by a decrease in b-potential. Recovery in b-potential is reached before recovery in blood pressure is recorded.

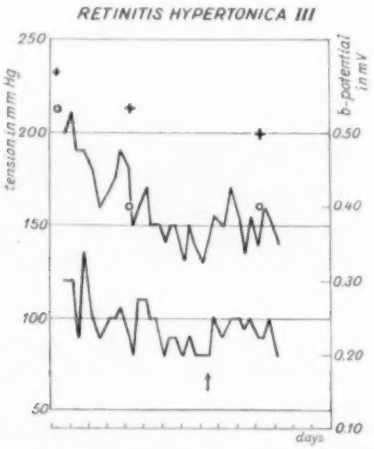

Fig. 8.—Influence of rest and diet on the blood pressure and the b-potential of the ERG. Circles mark the curve for the right eye; crosses, the curve for the left eye. The arrow indicates that the patient is allowed to walk about.

We are inclined to believe that such a normalization in the supernormal electrical response points to an amelioration of the thus far abnormal retinal metabolism, following, for instance, the abolition of retinal angiospasms.

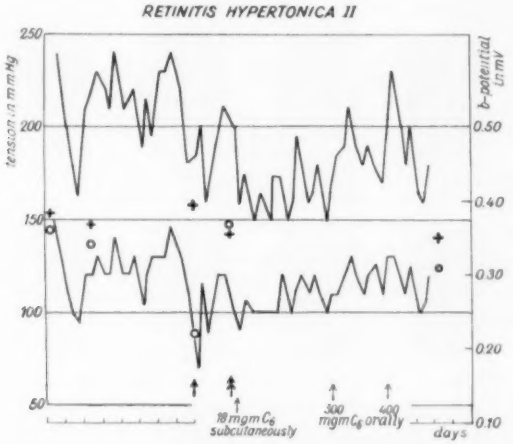

Fig. 9.—Insignificant effect on electrical responses of major variations in blood pressure. Circles mark the curve for the right eye; crosses, the curve for the left eye. Arrow and double arrow indicate test doses of hexamethonium and alkavervir, respectively.

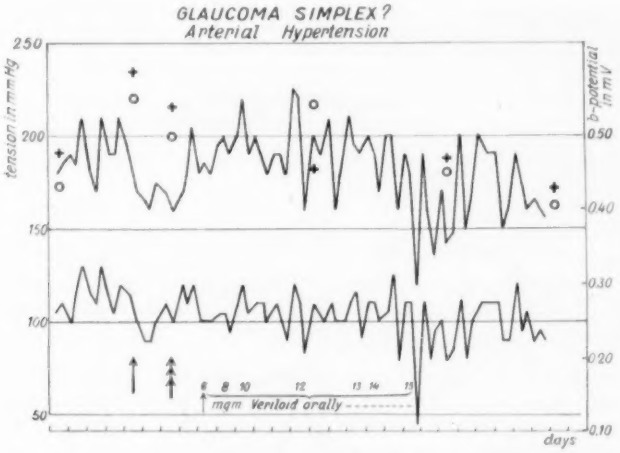

Fig. 10.—Curve for blood pressure under the influence of conservative therapy and under alkavervir therapy. Major variations in the b-potential of the ERG. Curves, discussed in Figures 5 and 6, were taken at the dates marked by arrow and double arrow, respectively.

An identical effect was recorded in a patient suffering from hypertensive retinopathy, Grade II, in whom after sympathectomy the supernormal ERG changed into a normal one. However, when, several months later, the blood pressure rose again, the normal response returned to a supernormal one.[4]

In J. H., a woman aged 61, who was suffering from hypertensive retinopathy, Grade II, reduction in blood pressure was observed following conservative therapy, without, however, a significant alteration in the normal ERG (first part of curves, Fig. 9). Over a period of seven

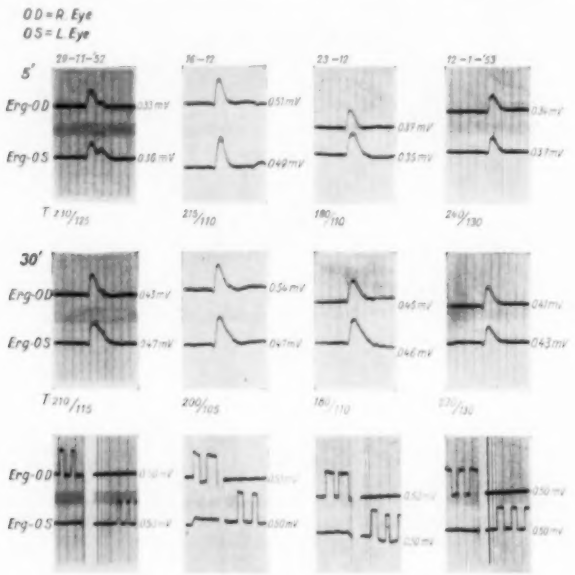

Fig. 11.—Marked variations in electrical response after five minutes of dark adaptation and rest. Variations are less marked after a period of 30 minutes in the dark room. Same patient as that referred to in Figures 5, 6, and 10.

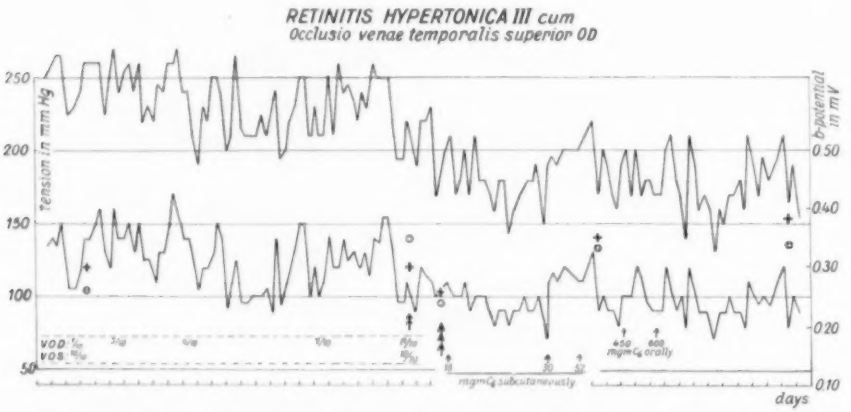

Fig. 12.—Influence of rest and adequate diet on visual acuity. Effect of hexamethonium on blood pressure and electrical response of the retina. Curves, discussed in Figures 1 and 2, were taken at dates marked with double and triple arrows, respectively.

days the blood pressure showed a reduction of from 240/150 to 175/110. The ERG, again, showed very little variation during the intravenous injections of hexamethonium and alkavervir, although the blood pressure varied considerably. The same holds true for the first few weeks

of hexamethonium therapy, during which time a marked alteration in blood pressure was unable to disturb significantly the normal electrical response.

In Figure 10 are shown the curves representing the blood pressure and electrical response of the retina of the patient discussed earlier (Figs. 5 and 6). Following the intravenous injection of hexamethonium and alkavervir, a marked change in electrical response was observed.

A similar variation was observed when records of the blood pressure and electroretinograms taken at short intervals were compared. This inconstancy in electrical response is remarkable, as illustrated in detail in Figure 11. With a more or less stable blood pressure, marked variations in electrical response were found at different times of recording and after the usual period of five minutes' preliminary rest in the dark room. After a prolonged rest in the dark of up to 30 minutes, however, these differences were less marked. A clear gain in height of the b-potential was demonstrable. Such a gain is, in our opinion, a sign of improvement in the metabolic condition of the retina. As one of us showed before,[4] such a gain is specific for minor atherosclerotic changes in the retinal vessels.

This patient, showing a general arteriosclerosis, was treated elsewhere for glaucoma simplex. However, we could never demonstrate intraocular hypertension. We diagnosed this case as one of pseudoglaucoma due to atherosclerotic changes in the retina and optic nerve.

In Figure 12 we give the curves for blood pressure and the values of the b-potential of the ERG recorded from the patient referred to in Figures 1 and 2. During a period of rest and diet, followed by successful treatment with hexamethonium, a marked reduction in blood pressure was observed. The electrical response, however, remained fairly constant. We are inclined to consider such a stable reaction, recorded over a period of several weeks, as prognostically favorable. It is remarkable that an improvement in visual acuity was obtained during a period of rest and adequate diet, before therapy with hexamethonium was started. The electrical response of the retinas showed a very stable reaction during the test injections with hexamethonium and alkavervir, as shown in Figures 1 and 2. The same holds true for the prolongation of the preliminary period of rest and adaptation in the dark room of from 5 to 30 minutes. We are inclined to believe that all these facts point to a stable metabolic condition of the retina, which makes, in our opinion at least, the prognosis in this case favorable.

COMMENT

When we compare the results obtained in different patients during the fall in blood pressure following an intravenous injection of hexamethonium or alkavervir, the difference in electroretinographic reactions is remarkable. In some patients even an extreme reduction in blood pressure within a few minutes was unable to provoke a significant change in the electrical response of the retina, e. g., Figure 4, whereas in others, showing an identical fall in blood pressure within the same lapse of time, a significant decrease could be observed (Fig. 5). Even when the reduction in blood pressure is not so marked, however, the b-potential of the ERG may show an appreciable decrease. In those patients who show a less stable electrical response following lowering of the blood pressure, it was shown that a prolongation of the preliminary period of rest and dark adaptation from 5 to 30 minutes was followed by an increase in the b-potential. Both these unstable electrical responses were found in those patients showing a marked arteriosclerosis. This observation is in perfect agreement with the findings of one of us [4] that in hypertensive sclerosis of the retina the hypertension is essential for the maintenance of a sufficient retinal oxygenation.

In cases of atherosclerotic hypertensive retinopathy, in which an increase in height of the b-potential follows a period of prolonged rest, we have to accept the idea of a recovery, at least partial, from the insufficient oxygenation of the retinal cells. This increase is demonstrated by comparing the records taken after the usual period of 5 minutes' rest and dark adaptation and those taken after 30 minutes of rest in the dark.

There is real danger in abolishing the hypertension, as is shown by the disturbance in the electrical response following antihypertension therapy discussed in the present paper.

When we consider in detail the relation between blood pressure and electrical response, as presented in Figure 7, it is remarkable that the blood pressure can fall to a very low level before the ERG follows its example. But if the threshold value is passed, the fall in b-potential is very steep. If we are allowed to conclude that there is a close connection between the height of the b-potential and the retinal oxygenation, as suggested previously,[4] it is likely that the retinal oxygenation is sufficient under normal circumstances but fails when the blood pressure is reduced below a critical level.

The height of this threshold value depends on the grade of atherosclerosis of the retinal vessels, as well as such influences as insufficient minute volume of the heart and insufficient oxygenation of the blood. Even when the blood pressure has recovered only partially from an injection of hexamethonium or alkavervir, a fairly complete recovery of the electrical response may be shown. The threshold value for sufficient retinal oxygenation has then been reached.

An increase in height of the b-potential following a prolonged period of rest in the dark room of up to 30 minutes, as well as instability in electrical response following a reduction in blood pressure, points, in our opinion, to a rather unfavorable prognosis of the retinal process. The same holds true for the presence of variations in b-potential under approximately the same conditions of blood pressure and recorded at different times (Fig. 11).

It seems to be important for the estimation of the retinal metabolism to investigate the following points: (1) the electrical response recorded after 30, as well as after 5, minutes of rest in the dark; (2) the electrical response following a reduction of blood pressure, at least to a level of 150/90, and (3) the electrical response at different times of recording. The more stable these response are, the more favorable, in our opinion, is the prognosis for the retinal process.

SUMMARY

Thirty-two patients suffering from arterial hypertension and showing various retinal complications were treated with hexamethonium and alkavervir (Veriloid).

The effect of a reduction in blood pressure on the electrical response of the retina was investigated.

Acute lowering of the blood pressure affected mainly the patients suffering from atherosclerosis of the retinal vessels and general arteriosclerosis.

The importance of hypertension for the maintenance of a sufficient retinal metabolism in these cases is stressed.

A poor diagnosis in cases of hypertensive retinopathy with/without atherosclerosis is indicated by (1) an electrical response which gains considerably in height after a prolonged stay in the dark of up to 30 minutes; (2) an electrical response which follows an acute fall in blood pressure to the level of 150/90, and (3) an electrical response which shows appreciable variations at different times of recording, although the blood pressure remains approximately constant.

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LID MOBILIZATION AND TARSORRHAPHY FOR MASSIVE PROPTOSIS

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THERE ARE several types of massive proptosis which constitute a dangerous threat to the eye. In such cases the cornea is exposed because the lids cannot close over it. This is followed by exposure keratitis, which may terminate in serious loss of vision, or even in loss of the eye. For a mild degree of corneal exposure there are a number of well-known techniques available, such as production of marginal lid adhesions and the Fuchs, Wheeler, and Kuhnt-Szymanowsky tarsorrhaphies. However, in the massive proptosis which may be encountered with some cases of thyrotropic exophthalmos, especially with orbital tumors, these measures may not be sufficient to protect the globe. Even when they are attempted in such cases, the lid sutures give way under the pressure and the cornea is again exposed. The procedure to be described has the great advantage that it produces a firm tarsorrhaphy and secures protection for the cornea in cases in which this is essential. In those cases of orbital neoplasm where the fifth and seventh cranial nerves are involved, such protection is urgent.

In many of those cases of proptosis in which the usual lid sutures or marginal adhesions cannot hold the lid together, it is almost impossible even to approximate the lid edges. Both lids may be under a tremendous amount of tension and cannot be mobilized sufficiently. The lower lid, which stretches less, is drawn taut into a sharp horizontal line which cuts into the proptosed globe, causing a great deal of cyanotic injection and chemosis of the exposed and prolapsed conjunctiva. Though the two lids have similar structures and attachments, the lower lid cannot be mobilized as well as the upper. This may be due to the fact that it is shorter both vertically and horizontally, has less anterior convexity, and stretches less.

The firm basic structure of each lid depends on the tarsal plate, situated deep to the fibers of the orbicularis oculi. The lateral margins of the upper and lower tarsi unite to form a conjoint lateral tendon, bound externally by a strong, taut lateral palpebral ligament to the orbital tubercle of the zygomatic bone, which lies on the lateral orbital wall, somewhat behind its anterior margin. Similarly, the medial margins of the upper and lower tarsal plates form a conjoint medial tendon, which is attached by a medial palpebral ligament to the upper half of the anterior lacrimal crest. Thus, the deeply recessed attachment of the medial palpebral ligament, as well as the recessed attachment of the lateral palpebral ligament, normally causes a snug coaptation of the lid margins against the globe and limits the mobility of the lids. With massive proptosis, the globe pushes against this taut tarsoligamen-

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tous barrier, with resultant corneal exposure and herniation of strangulated and cyanotic conjunctiva. To overcome this difficulty, we have developed a procedure by which the lid margins are approximated more easily.

PROCEDURE

Local injection of procaine with epinephrine is used for infiltration of the lids and lateral periorbital tissues. This is useful even with loss of sensation due to fifth nerve involvement, as some deeper sensation often remains. An incision is then made through the reflected conjunctiva at the lateral margins of the upper and lower fornices. A straight Stevens scissors is introduced parallel to the lateral wall and carried back for 8 mm. or so, with the blades open so as to straddle the external palpebral ligament, which is then cut, thus freeing the lateral conjoint tendon from its attachment to the lateral orbital wall. Several cuts may be necessary to free the lateral tarsal margins completely, and this must be accomplished in order to allow the mobilization of the skin around the lateral canthus, as will be described below. Bleeding may be copious, but is usually easily controlled with mild pressure and epinephrine.

The incision is then carried through the upper and lower fornices at the lateral borders. The upper and lower lids, together with their underlying orbicularis oculi fibers and tarsi, are then separated from the deep fasciae. The incision is extended to undermine the adjoining skin covering the muscles on the temporal and zygomatic bones, so as to mobilize the lateral portions of the upper and lower lids. For this purpose, it is usually necessary to carry out the undermining about ¾ in. (1.9 cm.) above the outer aspect of the lateral orbital margin and 1 to 1½ in. (2.5 to 3.8 cm.) directly laterally and below (Fig. 4*a*). In this way, the undermined tissues of the lids and the adjoining skin may be mobilized and made to lie loosely over the globe so that the tarsorrhaphy may then be done without undue tension on the lids. It is usually necessary to mobilize the lower lid more than the upper lid. In addition, it is helpful to do a lateral canthotomy through skin and lateral orbicularis tendon for a variable distance, from ¼ to ½ in. (0.6 to 1.3 cm.), in order to allow the tenser lower lid to move medially a little more than the upper one. The result is that some of the external skin lateral to the lower lid is brought in medially, and its edge approximates the intact lid margin of the outer aspect of the upper lid margin. The outer 2 or 3 mm. of the lower lid edge is denuded of its conjunctiva. The opposing portion of the upper lid edge is then denuded of its conjunctiva and the tarsorrhaphy then performed over rubber tubing. The outer portion of the upper lid margin is attached to the lower edge of the wound produced by the canthotomy and the denuded outer 2 or 3 mm. of the lower lid edge. The mobilization of the lower lid allows enough leeway to permit covering the globe adequately without tension, so that the sutures will not tear through. The prolapsed conjunctiva is replaced before the suture is tied. If it does not stay replaced, it is secured with a mattress suture through the lower cul-de-sac. For this purpose, a 0000 black nonabsorbable surgical (silk) mattress suture is taken through the lower cul-de-sac and brought out on the skin at the lower orbital margin, thus replacing the lower conjunctiva and re-forming the lower cul-de-sac. Several black silk sutures are used to coapt the upper and lower edges of the extended lateral canthotomy (Fig. 4*b*).

If more protection is needed, and it often is, an additional lid adhesion in the medial third of the lids can be performed at the same time. This is especially desir-

Fig. 1 (Case 1).—*A*, front view of massive proptosis with prolapsed conjunctiva. *B*, lateral view of proptosis with prolapsed conjunctiva. *C*, postoperative view following lid mobilization and tarsorrhaphy.

Fig. 2 (Case 2).—*A*, result of usual marginal tarsorrhaphy, with tearing through of medial adhesions and marked prolapse of conjunctiva. *B*, successful closure of lid, following lid mobilization and tarsorrhaphy.

Fig. 3 (Case 3).—*A*, marked proptosis and prolapsed chemotic conjunctiva. *B*, successful closure of lids several months after lid mobilization and tarsorrhaphy, and after recession of the orbital swelling following radiation therapy.

able in those cases in which the cornea remains exposed after the lateral adhesion is completed, or in a patient who is not fully conscious, to prevent him from injuring his eyes. When the sutures are removed, a small central interpalpebral fissure remains, which will allow vision if any is present (Fig. 5*b*). The medial adhesion can be opened later (Fig. 5*c*), especially if the original lesion in the orbit is such that recession of the swelling occurs, as with radiotherapy successfully applied to neoplastic invasion of the orbit. This procedure is intended primarily for those cases in which the tarsorrhaphy is planned as a permanent one. Thus, in malignant disease, even if recession of the swelling occurs, the patient usually does not mind

Fig. 4.—(*a*) Shaded area showing approximate area of undermining. The interrupted line indicates the lateral canthotomy carried through the skin and fascia beyond the external canthus. The cutting of the external palpebral ligament is not shown.

(*b*) Schematic illustration showing how the lower lid was displaced medially so that the outer lashes of the lower lid are now about 1 cm. more nasal than the outer lashes of the upper lid. The medial adhesion of the lid is not shown in this sketch but was carried out in all cases.

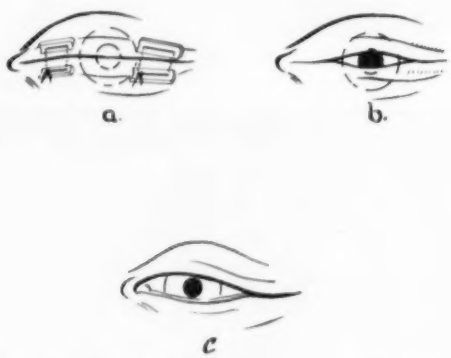

Fig. 5.—(*a*) Lateral and medial adhesions with sutures. (*b*) Sutures removed, showing small interpalpebral fissure, sufficient for vision. (*c*) Appearance after severing medial adhesions.

the tarsorrhaphy. If severe proptosis persists, or perhaps even increases, the tarsorrhaphy is certainly important for adequate protection of the globe.

While we have used this procedure only in proptosis due to neoplasm, we believe it will answer the same purpose in thyrotropic proptosis in which the cornea and globe are threatened and the usual tarsorrhaphy is ineffective. A Naffziger or other types of decompression might be avoided. Again, in thyrotropic proptosis, even if some recession takes place, it is usually incomplete, and this tarsorrhaphy would give a desirable cosmetic effect.

This procedure was used with satisfactory results in six cases. Three of these will be described.

CASE 1 (A. F.).—White man, aged 55, with carcinoma of the pharynx, and massive proptosis of the left eye due to orbital and retro-orbital metastases. The usual marginal lid adhesions were attempted but tore through almost immediately. The appearance of the patient's left eye on July 10, 1946, is shown in Figure 1*A* and *B*. On July 15 the procedure described in this paper was performed, and a photograph taken on July 24 shows the tarsorrhaphy completed, with the eyeball fully protected (Fig. 1*C*).

CASE 2 (J. S.).—Negro man, age 61, with squamous-cell carcinoma of the right antrum and extension to the right orbit and retro-orbital area. On Feb. 13, 1946, the usual marginal adhesions were attempted, but the medial adhesions soon gave way, and on March 5 the eye appeared as in Figure 2*A*. On April 22 the lid mobilization and tarsorrhaphy described in this paper was performed. The lids remained edematous, but the closure was satisfactory. In July, 1946, the lids still had good adhesion, with complete protection of the globe, despite the fact that the neoplastic process progressed intraorbitally (Fig. 2*B*).

CASE 3 (A. R.).—A white man, age 27, had a meningioma of the left middle fossa. In May, 1947, a craniotomy was performed; owing to excessive bleeding, only a partial removal was possible. After this, the patient showed an even greater proptosis of the left eye, with a good deal of chemosis and prolapse of the conjunctiva (Fig. 3*A*). In July, 1947, the lid mobilization and the modified tarsorrhaphy for massive proptosis described in this paper was performed, thus affording good coaptation of the lid edges and protection of the globe. Unfortunately, no pictures were obtained immediately after this tarsorrhaphy procedure. However, following a good deal of radiation therapy there was a recession of the orbital reaction, and the proptosis receded, leaving the eye well protected during this stormy period. Figure 3*B* shows the eye in November, 1947, when, following the radiotherapy, there had been a good deal of recession of the orbital reaction, and the globe remained well protected by these lid adhesions.

CONCLUSIONS

In cases of massive proptosis due to neoplastic or thyroid disease, the usual types of tarsorrhaphy are often inadequate to afford proper protection of the globe. In such cases, a method is suggested which cuts the external canthal ligament and undermines the outer portions of both lids sufficiently to mobilize the lids, especially the lower lid, with easier and more satisfactory approximation of the lid edges. This procedure should be reserved for those cases in which one does not expect to undo the tarsorrhaphy completely at any time in the future. So far, we have used it only in neoplastic orbital disease and have obtained satisfactory results. However, we believe it is also applicable to severe cases of thyrotropic proptosis.

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METASTATIC CARCINOMA TO EYE FROM BREAST

Effect of Endocrine Therapy

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THE PRESENT report concerns a patient who had a remarkable arrest and partial resolution of a metastatic carcinoma of the choroid with estrogen therapy. Eventually the tumor recurred in the iris and elsewhere in the eye, sparing relatively the original site of the ocular metastasis, and the eye was enucleated.

Metastatic tumors of the breast have been treated frequently in the past decade by castration, by androgens, and by estrogens, with varying but occasionally dramatic success. The mode of operation of these forms of therapy is obscure—indeed, at times these same agents appear to accelerate the growth of the cancer—but there is histologic evidence of a dual effect: early dissolution of the collagen about the tumor cells, with replacement by a fibrillar tissue, and necrosis of the cancer itself. Most amenable to this form of therapy are the more highly differentiated tumors and those having a compact connective tissue framework. Yet not all cells in any one tumor are equally affected, and recurrence is invariable after a remission of several months or years.[1]

A case of metastatic breast carcinoma in the choroid of the two eyes treated by castration was reported by Ellis and Scheie.[2] The choroidal lesions, which had been elevated 8 D., were flattened out and replaced by connective tissue within two months after castration. There was a relapse in three months, however, and the patient died eight months later despite testosterone therapy. A patient with metastatic carcinoma to the iris treated with estrogen was reported by Schlagenhauff,[3] but the effect of hormone treatment could not be assayed because of simultaneous treatment with x-rays and because the patient died shortly after institution of treatment. Nevertheless, these two cases appear to be the only ones reported heretofore in which metastatic lesions of the eye have been treated endocrinologically.

REPORT OF A CASE

The patient, (A. D. 391576) a 51-year-old woman, had first been seen at the Massachusetts General Hospital 10 years previously with a mass in the right breast, known to have been present for two weeks. The mass consisted of a hard, nontender, lemon-sized tumor in the upper outer quadrant of the right breast and showed a dimpling of the overlying skin and retraction of the nipple.

The patient had had two uncomplicated pregnancies. Menses were still regular, and there was nothing of note in the past history. Physical examination revealed no significant abnormality except for the breast. X-rays of the spine, pelvis, and lungs showed no metastases.

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Local removal of the tumor showed it to be malignant, and a right radical mastectomy was done. Axillary lymph nodes removed at that time were found to be carcinomatous. Accordingly, x-ray therapy was instituted, and 1,800 r (200 kv.) was given to the right axilla and 1,800 r to the right supraclavicular area.

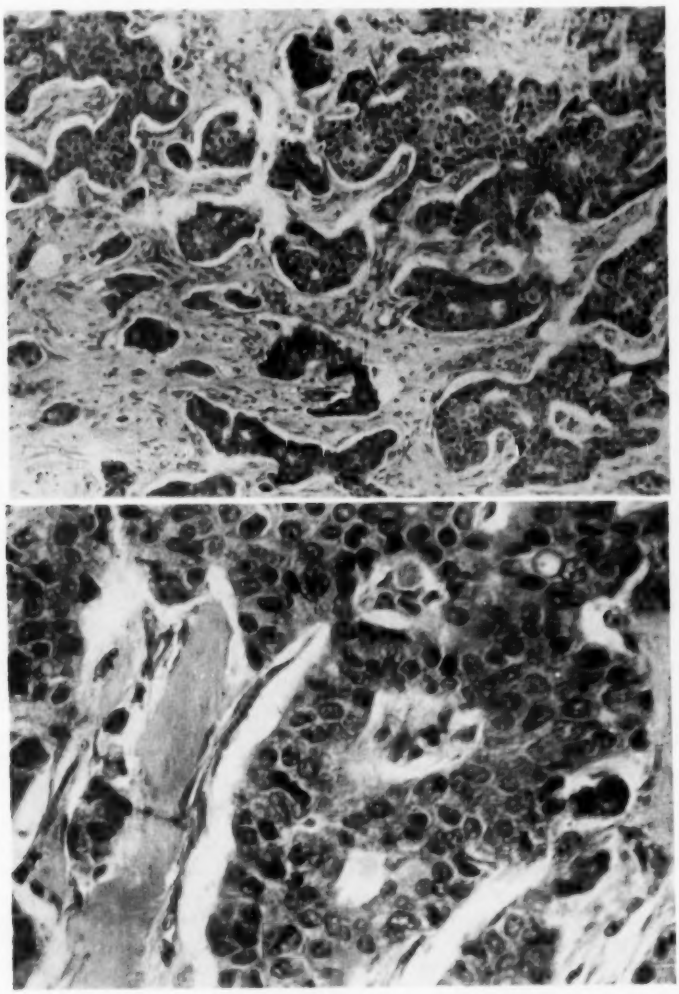

Fig. 1.—Sections of tumor removed from the breast: *A*, × 60; *B*, × 240.

Histologically, the breast tumor consisted of well-differentiated cells grouped in some places with little stroma, but having a thin capsule of connective tissue; in other places there were cords of epithelial cells with considerable connective tissue stroma or fat (Fig. 1). Occasionally these cells were arranged about a central lumen, suggesting acini. The mitoses were common but not abundant. There was some variability in staining but no necrosis.

The tumor was classified as a predominantly medullary carcinoma of the breast.

The patient was subsequently followed at periodic intervals and was never found to have a local recurrence. However, five years after the operation she developed a cough, chest pain, and some embarrassment of respiration. X-rays revealed fluid in the right chest, and a thoracotomy was done several times, with removal of 500 to 800 cc. of yellow fluid each time. The fluid contained large, immature cells suggestive of malignancy. Subsequent x-rays of the chest showed, in addition to the fluid, an oval area of increased density in the apex of the right middle lobe and a small area of increased density in the left hilus adjacent to the left upper bronchus. Skull and pelvis x-rays showed nothing abnormal.

The patient was given testosterone propionate, 50 mg. a day for two weeks and then continued on a dosage of 100 mg. three times a week. In three months the x-rays showed the lesions in the chest to be larger and there was fluid in the chest. The liver was then noted to be enlarged, and a few supraclavicular nodes were palpable. There was moderate hirsutism, hoarseness, and increased libido.

About this time the patient noted loss of vision in the left eye. Examination showed externally an unusual prominence of some of the larger conjunctival vessels of the left eye. Ophthalmoscopically there was in the left eye a ballooning separation of the retina in the upper temporal

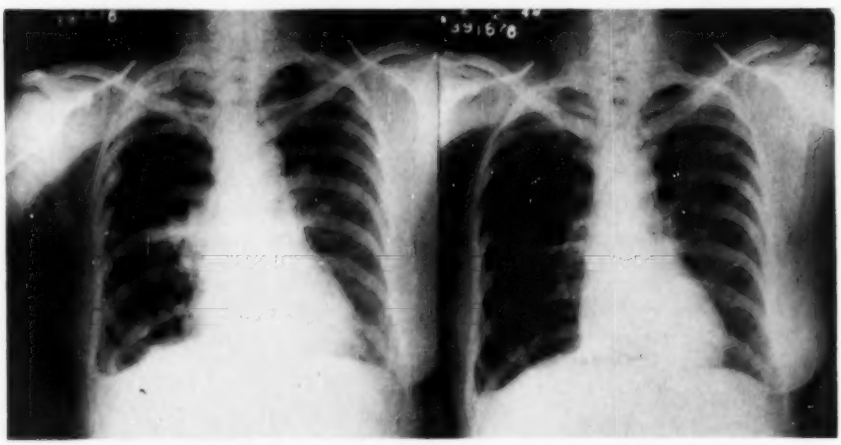

Fig. 2.—X-ray pictures of chest just before starting the diethylstilbestrol therapy (left side) and three months after starting the diethylstilbestrol therapy (right side). A comparison of the two pictures shows a striking resolution of the lesions in the chest.

quadrant, encroaching on the pupillary area, with edema and hemorrhage in the macula and a flat separation of the retina in the lower fundus. Transillumination of the eye was poor. The right eye was entirely normal.

There seemed little doubt that the eye lesion was metastatic and that the pulmonary lesions were progressing. Since this advance had occurred despite continuance of the testosterone, the hormonal treatment was changed to diethylstilbestrol. This therapy was begun at a dose of 15 mg. a day and increased to 400 mg. a day. In two months the vision had improved subjectively; the mass in the upper outer quadrant of the eye had decreased perceptibly, but there was still a flat separation of the lower retina and edema of the macula. The visual acuity, which, unfortunately, had not been recorded previously, was now 5/200 in the left eye. Visual fields showed a scotoma in the lower nasal quadrant, corresponding to the tumor, and a scotoma of much of the upper half of the field, corresponding to the separation of the lower retina.

Three months after start of the estrogen therapy the mass in the fundus had receded to approximately one-third its original size and had a predominantly white color. The pulmonary nodules (Fig. 2) had diminished markedly and the fluid in the chest had cleared. The hirsutism and libido had decreased and the patient felt generally well. Treatment was continued on 400 mg. of diethylstilbestrol daily. This dose was later reduced to 300 mg. daily.

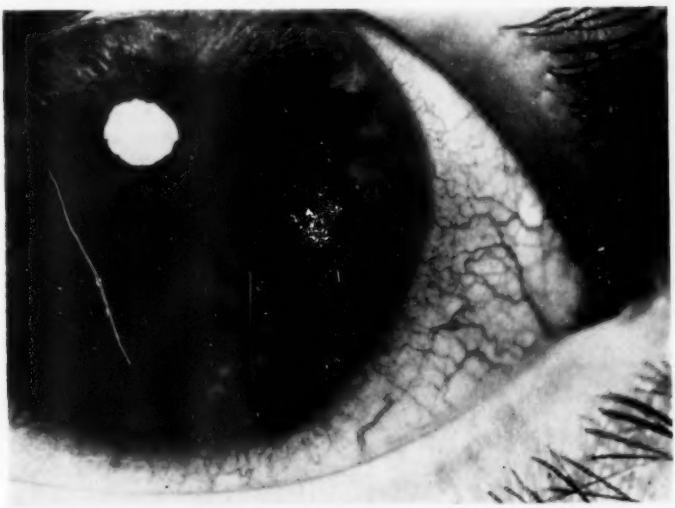

Fig. 3.—Appearance of the eye just prior to enucleation.

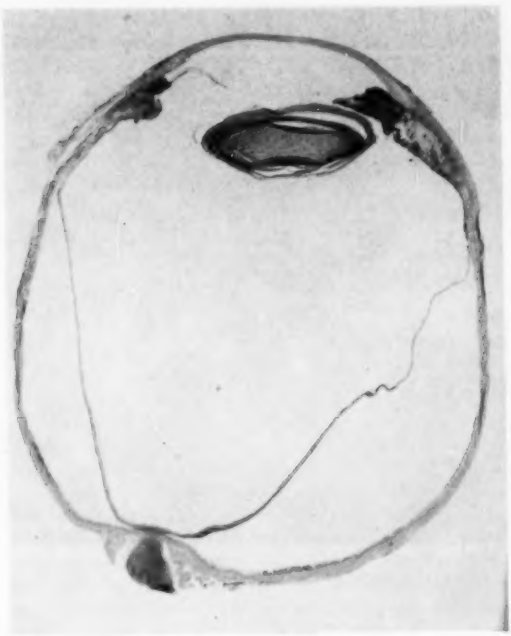

Fig. 4.—Cross section of eye in the region of the horizontal meridian. Tumor is especially evident in the angle of the anterior chamber. The separation of the retina is a postmortem artifact.

Six months after the beginning of the diethylstilbestrol therapy the fundus mass had further decreased and was showing pigmentation at its border. There was no longer any separation of the retina. The conjunctival vessels of the left eye were still prominent, as had previously been noted. Vision had improved to 20/200, but the macula showed drüsen in a honeycomb distribution.

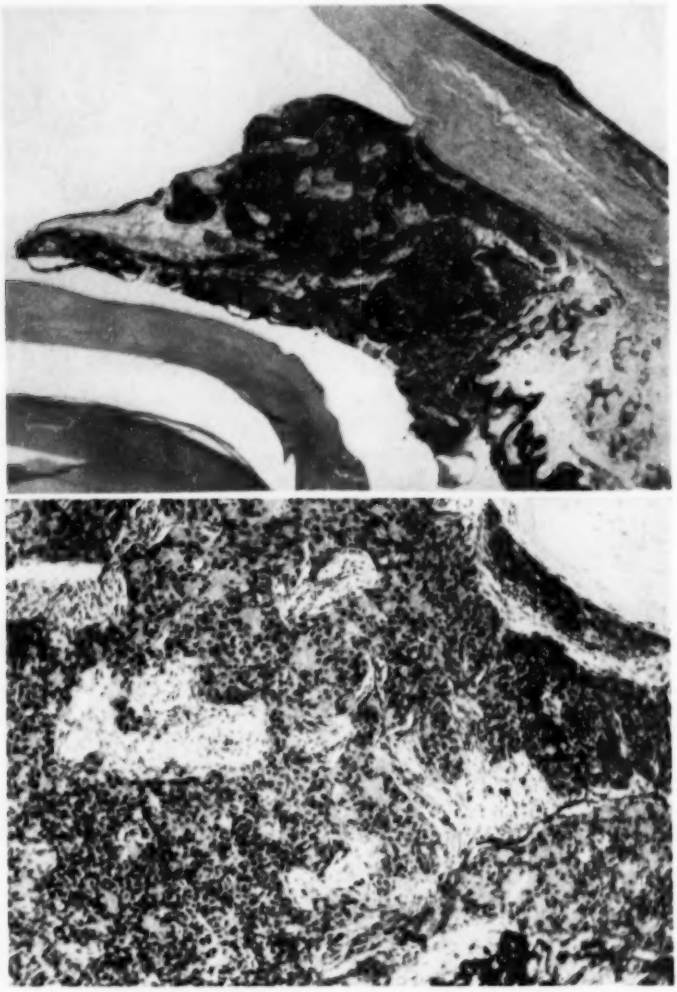

Fig. 5.—*A*, tumor filling the angle of the anterior chamber; × 38. *B*, higher magnification of the same tumor; × 60.

Fourteen months after start of the diethylstilbestrol the area of the fundus which had been elevated was found to be flat with a pigmented border. There was, however, roentgenologic evidence of a slight increase in the pulmonary metastases.

Two years after beginning of the diethylstilbestrol therapy, and three years after the mastectomy, the fundus picture was still that of a flat, white area in the upper temporal quadrant,

extending downward to just below the horizontal meridian. The pulmonary lesion had progressed, with evident pleural metastases, and fluid was present in the chest. At about this time the patient developed abdominal distress and was found to have ascites. Fluid withdrawn from the abdominal cavity showed carcinoma cells. She was castrated by x-rays, and the diethylstilbestrol was discontinued. After the omission of the diethylstilbestrol the patient had a single period of menstrual flow, lasting five days.

Two months following the castration there was considerable clearing of the lung fields and disappearance of the fluid in the chest. Five months after the castration the patient was gaining weight and felt well except for hot flashes and nervousness.

Eight months after the castration the left eye became uncomfortable and sensitive to light. On examination nothing was found other than the residual chorioretinal lesion; nor was anything further found in the eye 16 months after the castration. However, when the patient was examined 20 months after the castration, a tumor was noted in the angle of the anterior chamber of the left eye. This was a grayish mass, extending from 2 to 5 o'clock, and lay between the iris and the posterior surface of the cornea. It was lobulated and vascular but not pigmented or cystic.

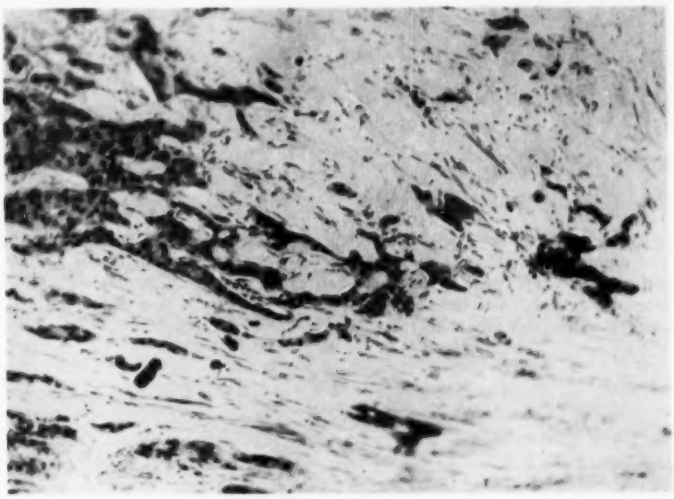

Fig. 6.—Tumor cells within the ciliary body; × 60.

There was a moderate number of cells in the anterior chamber, widespread adherence of the iris to the lens, and an outstanding beam to the aqueous humor. Although the fundus could be seen only indistinctly, there was definitely no elevation of the retina. The patient was given 1% diethylstilbestrol drops and atropine for the left eye.

Four weeks later there was no detectable change in the size of the tumor, but eight weeks after the local use of diethylstilbestrol was started the tumor of the anterior chamber had definitely increased and another nodule had appeared in the opposite side of the anterior chamber. The patient was given ethinyl (Estinyl) estradiol, 1 mg. three times a day, but in three months the tumors had further increased in size (Fig. 3) and the patient was having considerable pain in the eye. The outstanding abnormalities, aside from the tumor masses, were the colloidal aqueous, the presence of cells in the anterior chamber, the almost complete posterior synechia, the vitreous opacities, the normal tension, and the absence of any elevated mass in the fundus, so far as could be ascertained through the cloudy media.

The eye was enucleated on account of pain. The patient has been followed for one year since this time. There has been slight progression of the pulmonary lesion. It may be noted that the following chemical determinations on the blood, taken at the last visit, were representative of similar determinations taken throughout the course of the disease: calcium, 9.3 mg.; phosphorus, 3.7 mg., and alkaline phosphatase, 4.5 units, per 100 cc.

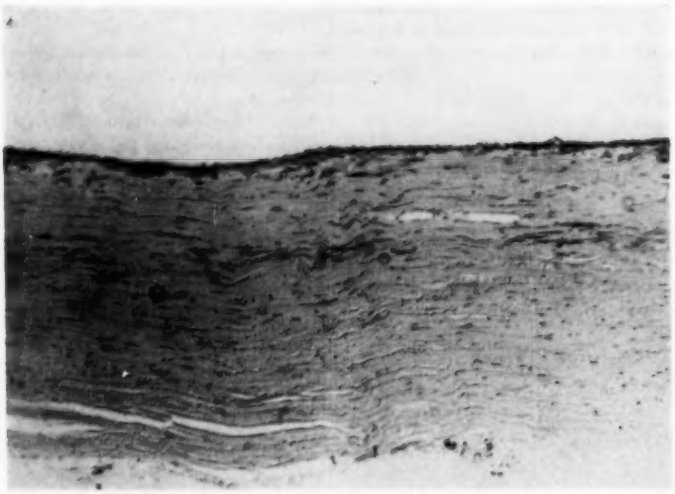

Fig. 7.—Area of eye in equatorial region corresponding to the site of the original tumor (× 60). The pigment epithelium is the dark line in the upper portion of the picture, and the sclera comprises the fibrous tissue of the lower half of the picture. The choroid has been extensively replaced by connective tissue showing a few blood vessels and a few tumor cells and merging almost indistinguishably with the sclera.

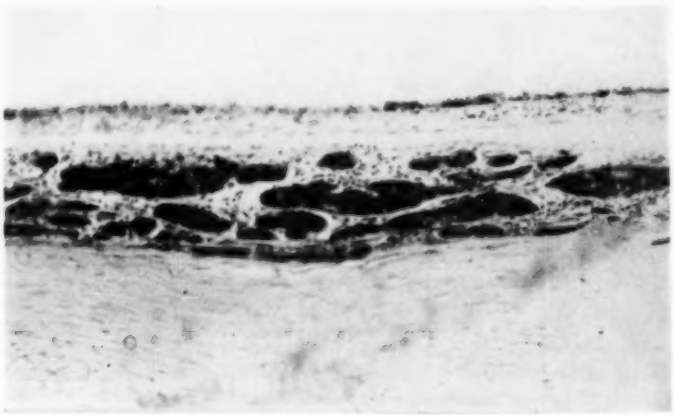

Fig. 8.—Tumor in choroid at posterior pole of eye (× 60). In addition to the tumor cells, the relatively normal architecture of the choroid is noteworthy.

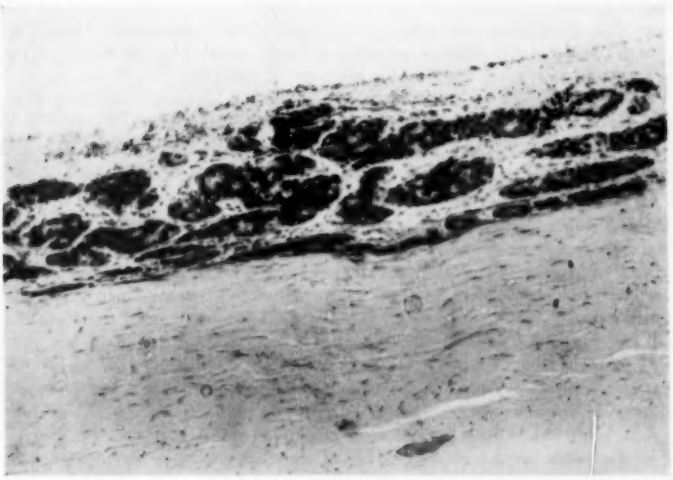

Fig. 9.—Tumor in choroid at nasal equatorial region (× 60). This area is to be compared with that on the opposite side of the globe pictured in Figure 7, which was the site of the original metastasis.

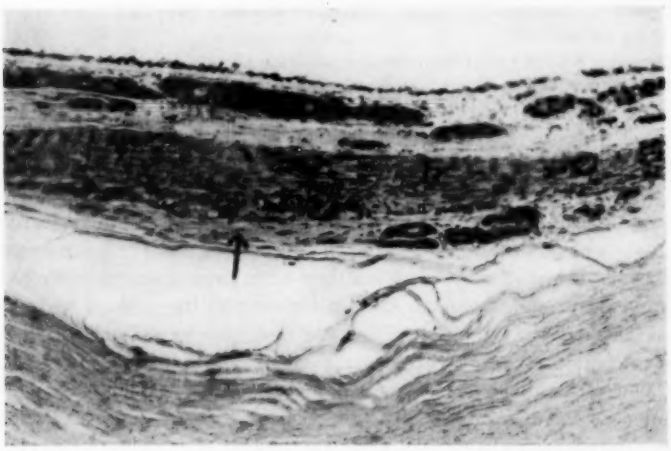

Fig. 10.—Portion of the choroid behind the equator on the nasal side, showing tumor cells infiltrating the long posterior ciliary nerve in the region indicated by the arrow (× 60). The sclera is largely separated by artifact.

The findings on pathologic examination of the enucleated eye were as follows:

The globe was of normal size and shape.

The gross abnormality noted on cross section of the eye was a tumor mass filling the angle of the anterior chamber on its temporal side (Fig. 4).

Histologically, the cornea and anterior sclera were not remarkable. Tumor was present, however, in the angle of the anterior chamber on both sides. This apparently arose from the substance of the iris or from the anterior portions of the ciliary body and grew forward to occlude completely the angle in sections cut just above the horizontal meridian (Fig. 5). The tumor consisted of masses of fairly well-differentiated cells separated by connective tissue septa.

The ciliary body also contained some masses of tumor within its substance and on its surface, but here the predominant arrangement of the tumor cells was in the form of cords, with an abundant connective tissue stroma and acellular collagen (Fig. 6).

The choroid showed some tumor throughout its entire extent, but it is noteworthy that on the temporal side, where the mass had been originally noted clinically, it was largely replaced by dense connective tissue in which tumor cells were scanty (Fig. 7). Here the normal choroidal structure was completely lacking, and the dense connective tissue which replaced it merged almost indistinguishably with the sclera. There were a few strands of tumor cells within the stroma and an occasional blood vessel, but both were inconspicuous until the posterior pole was reached (Fig. 8), that is, away from the region of the original tumor mass. Although the choroid was thus entirely replaced on the temporal side by dense connective tissue, the pigment epithelium was an intact membrane, showing only slight diminution in its pigment content, and there was remarkably little alteration in thickness of the choroid. Nor were there any adhesions of the retina to the choroid. This is surprising in view of the large mass which presumably occupied this region prior to the estrogen therapy.

The choroid of the posterior pole of the eye and of the nasal side of the globe showed normal choroidal structure with irregular but abundant infiltration by small masses of tumor similar to that in the iris and ciliary body (Fig. 9). The stroma between these masses was a loose meshwork, characteristic of the normal choroid. The long ciliary nerve in the choroid on the nasal side showed infiltration by tumor (Fig. 10); this may have had some bearing on the pain which the patient had.

The sclera was normal except for extension of tumor along a few emissaria in the posterior portion of the globe. Yet no tumor was found actually outside the globe.

The retina, separated by artifact, showed no abnormality other than some invasion by pigment cells in its temporal periphery. Nor was the optic nerve or its sheath abnormal.

COMMENT

The present patient, who had initially a predominantly medullary carcinoma of the breast, showed no beneficial effect on the metastases when testosterone was used but did show a dramatic response for a time with large doses of diethylstilbestrol. This improvement applied both to the ocular lesion of the choroid and to the pulmonary metastases. Nevertheless, subsequent histologic examination of the choroid showed it to contain extensive carcinoma, even though it appeared to have resolved clinically. One of the more interesting aspects of the case is the fact that recurrence of the tumor involved, preferentially at least, a portion of the eye other than the site of the original metastasis. This obviously limited observation suggests that the estrogen therapy had made the original metastatic site unsuitable for growth of the tumor, presumably through the laying down of dense connective tissue.

SUMMARY

A case is presented in which the patient had a tumor of the breast with extension to the axilla. Despite a mastectomy with dissection of the axilla, metastases to the lungs and to one eye developed five years later. The metastatic lesions increased

despite testosterone propionate (50 mg. a day for two weeks, followed by 100 mg. three times weekly for three months), but with diethylstilbestrol (beginning at 15 mg. a day and increasing to 400 mg. a day) there was marked clinical resolution of the choroidal and pulmonary lesions. This improvement persisted for at least two years. With subsequent reactivation of the pulmonary lesions and occurrence of metastases in the abdomen, the patient had an x-ray castration. Twenty months later, metastatic nodules appeared for the first time in the iris, although the original tumor site in the choroid remained flat. The eye was enucleated and found to contain proliferating carcinoma in the anterior chamber, apparently coming from the iris, and a diffuse carcinomatosis throughout the entire choroid, but relatively sparing the site of the original metastasis in the eye.

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LATE EMPTYING OF ANTERIOR CHAMBER AND CHOROIDAL DETACHMENT IN CATARACT OPERATIONS

Role of Internal Hernias of the Vitreous Body

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I HAVE been interested for some time in the appearance of late emptying of the anterior chamber (with or without choroidal detachment) in certain cases of cataract operations, even when the wound appeared hermetically sealed with three firm corneoscleral sutures.

The accepted explanation that the emptying of the anterior chamber is caused by leakage of aqueous humor in some part of the wound appears plausible in certain cases, since in these it coincides with the removal of the stitches. In other cases, however, doubt is thrown on this explanation by the fact that the wound appears entirely sealed, as tested by the use of fluorescein. In these cases it has been thought that the emptying of the anterior chamber is produced by detachment of the choroid. Emptying of the anterior chamber does occur, however, in the absence of detachment of the choroid in cases in which postoperative convalescence up to the time of the emptying of the chamber appears to be completely normal.

Various explanations of the pathogenesis of detachment of the choroid have been offered. Thus, Duke-Elder states [1]:

> Post-operative choroidal detachments persisting or occurring some days after operation are due to delayed closure of the wound or the subsequent rupture of its loosely adherent margins, whether it is a corneal section or the conjunctival flap of an operation for glaucoma. . . . Frequently some leakage from the wound can be demonstrated by the presence of a green stain after the instillation of fluorescein.

On the other hand, Arruga [2] attributes the detachment of the choroid to "subchoroidal hematomas whose genesis appears to be ex vacuo congestion of the choroid."

Stallard [3] seems to be partial to Fuchs's theory when he states that the choroidal detachment "is probably due to slight separation of the ciliary body, aqueous seeping posteriorly into the supra-choroidal space." Should the detachment of the choroid continue for several weeks, he advises a diathermic puncture to empty the subchoroidal serous fluid.

Blaskovics and Kreiker,[4] in referring to delayed wound healing, state:

> In its mildest form, though not the least dangerous, this complication is manifest in a delayed recovery of the anterior chamber without a visible opening of the wound. Normally the chamber re-forms within 24 hours and continues thus. At times the chamber does not re-form until the fifth or sixth day, without any known cause, such as embedding of the vitreous or capsular

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remains or detachment of the choroid, to explain the delay. The intracapsular extraction appears to assist this delay, and in this sense the most unfavorable cases appear to be those of extraction in toto with total iridectomy.

In dealing with the delay in the formation of the anterior chamber, Stallard [3] also establishes its greater frequency in the intracapsular operation. He states:

It may be due to sudden emptying from trauma or straining; a leaking wound; a failure of the wound to heal in old decrepit people; and to a large choroidal detachment.

In other words, he considers the two mechanisms which have been recognized as causing emptying of the anterior chamber, namely, leakage of aqueous through the wound and detachment of the choroid.

I believe that I have found the cause of emptying of the anterior chamber in those cases in which, as Blaskovics states, there is no detachment of the choroid or visible opening of the wound which can be blamed for it. I have been able to study two cases which have led me to the following theory:

Herniation of the vitreous body through the pupil into the anterior chamber (without rupture of the hyaloid), if of sufficient volume, expresses the aqueous

Fig. 1.—*A*, aphakic eye with flat vitreous face; *B*, incomplete hernia; *C*, complete hernia with flattening of the anterior chamber.

humor and makes contact with Descemet's membrane. On sliding forward, the vitreous draws forward the iris diaphragm (Fig. 1 *C*). The flattening of the anterior chamber is thus brought about without leakage through the operative wound or detachment of the choroid, as occurred in Case 1. This situation is somewhat similar to that of an abdominal hernia. The abdominal opening, or ring of the hernia, is represented in the eye by the pupillary aperture; the sac of skin receiving the hernia, by the anterior chamber; the contents of the hernia (intestine and omentum), by the vitreous prolapsed into the anterior chamber. The hyaloid membrane, which limits the herniated vitreous, has its equivalent in the parietal peritoneum which surrounds the herniated viscera.

It is easily understood that, as in the abdomen, the following factors will assist the hernia of vitreous into the anterior chamber: (1) increase of vitreous pressure (equivalent to the increase of the abdominal pressure by coughing or effort): a voluminous or turgescent vitreous, a raising of the pressure in the vitreous by coughing, vomiting, or muscular effort, and (2) dilatation of the pupil or a broad iridectomy (equivalent to the pathological expansion of the abdominal hernia ring).

Case 2, which originally showed a vitreous hernia with emptying of the anterior chamber, without any detachment of the choroid at the start but with subsequent development of a choroidal detachment, led me to believe that the emptying of the anterior chamber could be caused by the vitreous hernia; that is, I concluded that the detachment of the choroid was not the original cause of the emptying of the anterior chamber, but was secondary to it, and that the emptying was brought about by the vitreous hernia. I was at first of the opinion that the vitreous hernia in the anterior chamber left a vacuum in the vitreous chamber, which pulled on the choroid. In this connection, the solid adhesion which exists between the vitreous and the pars plana of the ciliary body should be recalled.

Wolff [5] gives the following description:

The vitreous lies in contact but only slightly adherent to the retina. It is, however, attached to the optic disc, and more especially to the ciliary epithelium in a zone 1.5 mm. broad immediately adjacent to the ora serrata. This area is known as the base (Salzmann) or origin (Wolfrum)

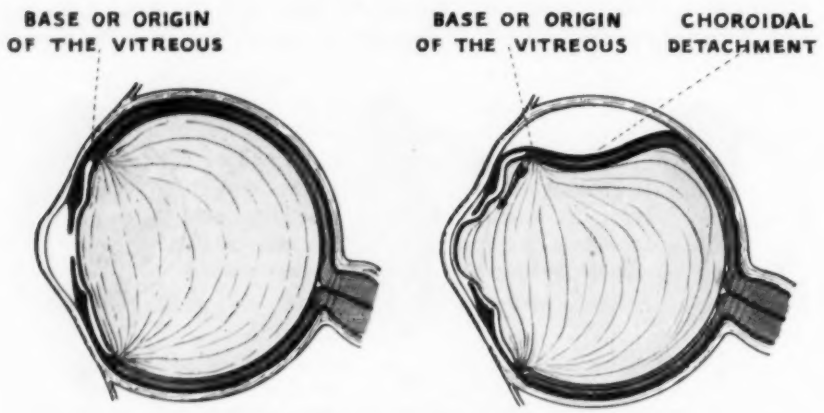


Fig. 2 (left).—Aphakic eye without vitreous hernia.
Fig. 3 (right).—Vitreous hernia, causing flattening of the chamber and choroidal detachment.

of the vitreous, for it is here that, as a result of fixation or hardening fluids, or under pathological conditions, the vitreous remains adherent. Even severe injuries do not tear the living vitreous from this situation and when it does give way it takes part of the ciliary epithelium with it (Salzmann). Also, as will be seen later, all vitreous fibrils can be traced back to this region.

Duke-Elder,[6] in his chapter on the anatomy of the vitreous, gives a figure showing the isolated vitreous body with a ring of the pigment epithelium of the ciliary region which remained adherent to the vitreous on being detached from the coats of the eye.

We have, therefore, an important anatomical argument in favor of the idea that the vitreous hernia into the anterior chamber can in certain cases loosen the choroid by direct traction through this physiological adhesion, the base or origin of the vitreous (Fig. 3). The reason that traction generally produces a detachment of uvea, and not a retinal detachment, is that this vitreous adhesion is situated immediately in front of the ora serrata (in a zone 1.5 mm. in width), that is to say, at the rear of the pars plana of the ciliary body.

It is also interesting to note that the choroid adheres firmly to the margin of the optic disc and is more or less attached at the level of the entrance of the four venae vorticosae. There is no other firm adherence to the sclera over the rest of its surface. The lamina of the suprachoroid, or lamina fusca, is more compact posteriorly than anteriorly, a fact which would explain, according to Wolff, the habitual anterior situation of the detachments of the choroid. Detachment of the anterior part of the ciliary body is more difficult to produce, since this portion is suspended by the anterior ciliary arteries and the long posterior ciliary arteries.

REPORT OF CASES

CASE 1.—Albert F., approximately 60 years old, private patient.

In 1951 the patient received a sharp, perforating corneal wound in the right eye, leaving a corneal nebula at 3 o'clock adjacent to the limbus; this was followed by protracted iritis.

In May, 1953, the patient consulted me for bilateral cataract. Vision was equal to light perception in the right eye and to counting fingers at 40 cm. in the left eye. It was decided to operate on his left eye, which was not affected by the iritis.

On June 1, operation was performed on the left eye. Incision with knife, resulting in small conjunctival flap only in the external third. Two corneoscleral sutures (one internal, the other central) and an external conjunctival stitch at the small flap. Peripheral iridectomy at 1 o'clock and iridotomy at 11 o'clock. Intracapsular extraction with forceps. Very resistant zonule and adhesion of the posterior face of the iris to the inferior external sector, owing to which the lens bore fragments of the pigmentary coat in this zone. No loss of vitreous. Air injection in the anterior chamber. Neither a miotic nor a mydriatic was instilled on completion of the operation.

During the first days the postoperative course was very satisfactory, with the eye practically white and a deep chamber. The air bubble was absorbed within three days.

On the fourth day, when the eye showed a round, central, and miotic pupil, atropine was instilled for the first time. Even though the patient was kept in bed, with a binocular bandage, he complained of pain on the following night, for the first time. Examination showed a mydriatic pupil and complete flattening of the anterior chamber, in spite of good coaptation of the wound margins.

I looked especially for a choroidal detachment, but the fundus reflex was normal in all directions.

The patient remained in bed, with binocular bandage and dressings of penicillin ointment only. Two days later the chamber again appeared deep and the pupil of normal size.

On June 12, the eye being in perfect condition, the stitches were removed, without loss of aqueous. During the biomicroscopic examination on the following day, it was seen that the vitreous appeared in the pupil, forming a slight sacculated protrusion (incomplete hernia), which penetrated the anterior chamber to a moderate degree and was seemingly strangled by the pupil (Fig. 1*B*). The chamber was deep, and the small hernia was distant from Descemet's membrane.

I instilled atropine twice a day, in the belief that the iris might adhere to the vitreous at the level of the pupillary strangulation.

Examination on the following day showed a totally flattened anterior chamber and a semimydriatic pupil. A complete vitreous hernia could then be observed with the biomicroscope, the narrow beam showing that it was in contact with Descemet's membrane (Fig. 1*C*). The wound appeared completely closed, and I again searched for a choroidal detachment but the fundus reflex was entirely normal.

The patient was ordered to keep in bed at home with a binocular bandage.

The examination done in his home two days later, on June 16, showed a 4 mm. pupil and a re-formed anterior chamber.

He was allowed up on June 17, and I prescribed aphakic lenses (sph. +14.00 D., there being no astigmatism), obtaining 20/40 vision. The biomicroscope again indicated that the

vitreous was forming a moderate globular protrusion, which appeared to be strangled at the level of the pupil, with hyaloid membrane halfway between Descemet's membrane and the iris (Fig. 1*B*).

With the idea in mind of avoiding adhesions between the iris and the vitreous, on June 19 (18 days after the operation) atropine was once more administered. On the following day the chamber was again flattened, while the vitreous hernia protruding through the semimydriatic pupil touched Descemet's membrane (Fig. 1*C*). The wound had healed completely (19 days after operation), and the fundus was absolutely normal.

It was only then that I was convinced that the vitreous hernia, by invading the anterior chamber after dilatation of the pupil, was the cause of the emptying of the chamber.

This time, both bed rest and use of miotics were ordered, and after 48 hours the chamber was deep and the hernia reduced, as before. The patient traveled south by train without any difficulties; he was instructed to instill pilocarpine twice a day, and not to use a mydriatic thereafter. Dr. Morales, who is managing the patient in Temuco, has reported 5/5 vision, the biomicroscope showing only a small, incomplete hernia through the miotic pupil. There has been no further emptying of the anterior chamber.

From this case I have arrived at the following conclusions:

1. The emptying of the anterior chamber was not accompanied by leakage of aqueous through the wound or by choroidal detachment.

2. The emptying of the anterior chamber occurred three times (the last being 19 days after operation, with the wound perfectly healed), that is, each time that atropine was instilled.

3. On these three occasions the emptying of the anterior chamber was accompanied by a considerable increase in the vitreous hernia (with mydriasis, the hernia was no longer supported by the iris), which came into contact with Descemet's membrane.

4. Both the vitreous hernia and the emptying of the chamber occurred repeatedly without there being any vestige of choroidal detachment. This occurrence proves that the detachment of the choroid does not produce the hernia or the emptying of the chamber by pushing the vitreous from behind.

In the question of which came first, the egg or the hen (the vitreous hernia or the choroidal detachment), it is suggested that the vitreous hernia is the primary phenomenon, as it can appear of itself without a choroidal detachment.

CASE 2.*—Manuel D., aged 72; obs. 40/2598, Salvador Hospital.

Diagnosis: Cataract in the right eye and exfoliation of the lens capsule. Left eye normal.

Vision was equal to seeing hand movements in the right eye, with tension of 13 mm. Hg.

The patient had a chronic cough, and in the preoperative period his tracheobronchitis had been treated with penicillin systemically.

Operation (May 4, 1953).—Right Eye: Incision with knife. Three corneoscleral sutures. Peripheral iridotomy at 1 o'clock and at 11 o'clock. Erysiphake extraction. No loss of vitreous. Air injection in anterior chamber.

Course.—Atropine was instilled, beginning on the day after the operation; there ensued an uneventful postoperative period, with a deep chamber. Ten days later the patient was allowed up, with his eye in perfect condition and the pupil mydriatic. The cough persisted in spite of the treatments.

* This patient was treated before the patient in Case 1, but the facts as presented could not then be explained. Only now, after my experience with Case 1, have I been able to understand what happened. For this reason, I have placed this case second in the series, even though chronologically it was the first.

On the following day (11 days after operation), on my visiting him to remove the stitches, he informed me that he had felt pain during the night. Examination revealed a red eye (previously the eye had appeared white) with totally flattened chamber and numerous folds in Descemet's membrane. The patient was examined with the slit lamp, and the following notation was made on his chart: Totally flattened anterior chamber; numerous folds in Descemet's membrane; globular vitreous, in contact with Descemet's membrane; no leakage of the wound, as revealed by use of fluorescein. Choroidal detachment was searched for in the dark chamber, but the fundus reflex was entirely normal (mydriatic pupil).

Rest in bed, binocular bandage, and atropine were prescribed. However, three days later there was still a flattened chamber, and a superior temporal choroidal detachment had appeared. The patient still coughed constantly. Rest in bed, use of binocular bandage, and atropine instillations were continued. The stitches were removed on May 25.

On May 29 (25 days after operation) the chamber was still flattened and the choroidal detachment more extensive. Biomicroscopic examination showed the pupil still mydriatic, with fine attachments to the vitreous hernia throughout its circumference.

In view of the possibility that a seclusion of the pupil was preventing circulation of aqueous from the posterior to the anterior chamber, thus hindering the formation of the latter, I decided to do an iridectomy and to inject air in the anterior chamber.

Operation (May 29).—Right Eye: Limbal incision ab externo of only 2 mm. at 10 o'clock. Fine forceps were used to grasp the iris and perform a total iridectomy. When I endeavored to inject air in the anterior chamber, the air was immediately expelled through the wound, and it was necessary to insert a corneoscleral suture, in spite of the small size of the incision. Air was again injected, and the ends of the thread were kept tense in order to close the wound instantly, thus preventing the leakage of air. A considerable bubble remained at the end of the operation.

Course.—On the following day the lower two-thirds of the air bubble had been absorbed, the chamber in this location being completely emptied. In the upper third a small air bubble still remained. Atropine was instilled for the last time.

On June 5 (seven days after the air injection) the chamber was slightly formed, but there was still a choroidal detachment.

On June 8 the chamber appeared somewhat deeper and the detachment of the choroid had disappeared.

The patient was discharged on June 16, with vision 3/40 with glasses, a shallow chamber, and a normal fundus reflex.

Case 2 suggests the following considerations:

1. Recurring cough probably favored the hernia of vitreous into the anterior chamber.

2. The persistent application of atropine in the postoperative period was a factor in this complication.

3. The emptying of the chamber coincided with the patient's leaving bed when the stitches had not yet been removed.

4. The biomicroscope showed a large vitreous hernia without choroidal detachment on the same day that the emptying of the anterior chamber occurred.

5. Three days later a detachment of the choroid was noted. Therefore, the choroidal detachment was not the cause of the vitreous hernia or of the flattening of the anterior chamber, but was probably its consequence.

6. The vitreous hernia prevented the air injection at the second operation, expelling the air outward in spite of the smallness of the wound (2 mm.). This suggests that the vitreous hernia is also capable of expelling the aqueous, even with the anterior chamber closed, through its normal drainage channels.

7. The knotting of the suture, together with the air injection, permitted the retention of a bubble in the anterior chamber, which, pushing the vitreous backward, contributed to the re-formation of the aqueous chamber and the reapplication of the choroid.

Case 3.—Tomas A., 79 year old; obs. 53/7759, Salvador Hospital.

Diagnosis: Bilateral cataract.

Operation.—Left Eye (June 30, 1953; Dr. Gormaz, surgeon): Incision with knife. Davies suture. Intracapsular extraction. Peripheral iridectomy. Air injection in the anterior chamber. Instillation of atropine once on the fourth day. Postoperative period without incident.

Course. Right Eye (July 9, or 10 days after operation on the left eye; Dr. Gormaz, surgeon): Same technique as that used on the left eye. Intracapsular extraction. No loss of vitreous.

Course.—The patient coughed a great deal from the third day after the operation. The chamber was formed, and the pupil was round and central. Atropine was instilled on the fourth day, and the patient was left with a monocular bandage. On July 15 atropine-cocaine-epinephrine drops were instilled into both eyes. On July 18, when the patient was due to leave the hospital, a choroidal detachment was found in the right eye.

On July 22, with Dr. Gormaz, I examined the patient and found in the right eye a globular vitreous hernia reaching Descemet's membrane, a shallow chamber, and a choroidal deteachment, forming a large temporal elevation and a smaller superior nasal one.

In the left eye, the pupil had a superointernal indentation. At this level vitreous filaments extended up to the operative scar; that is, there was slight rupture of the hyaloid membrane. In the rest of the pupillary area the vitreous face was flat, without prolapse into the anterior chamber. The chamber was deep. There was no choroidal detachment.

Case 3 permits the following considerations:

Two types of prolapse of the vitreous into the anterior chamber can be distinguished: (1) a lamellar form, to be found in cases of rupture of the hyaloid membrane, and (2) a saccular form, found when the hyaloid is intact.

In the patient's left eye there was only a slight prolapse, of the first type, at 10 o'clock, embedded in the operative scar. There was no saccular hernia or choroidal detachment in that eye.

However, in the right eye there was a hernia of the second type, with intact hyaloid, as in Cases 1 and 2. During the postoperative course the patient suffered from a severe cough. There was also the factor of instillation of the atropine-cocaine-epinephrine drops. In this eye, with a saccular hernia, a detachment of the choroid appeared.

Case 4.—Agustin S., 66 years old; obs. 52/11121, Salvador Hospital.

Diagnosis: Bilateral cataract.

On Sept. 23, 1952, an intracapsular extraction of the lens of the right eye was done, without incident (surgeon, Dr. Jaluff).

Atropine was instilled in the postoperative period. Seventeen days after operation flattening of the chamber and a detachment of the choroid were observed. Eight days later the patient was allowed to leave the hospital, with a deep chamber and no choroidal detachment. There is no record of biomicroscopic examination at that time, and it is therefore impossible to know whether there was or was not a vitreous hernia.

On July 9, 1953, an intracapsular extraction of the lens of the left eye was done, without incident (surgeon, Dr. Jaluff).

Fourteen days after the operation biomicroscopic examination showed a saccular vitreous hernia that almost touched Descemet's membrane. The anterior chamber was shallow, and there was no choroidal detachment.

This patient had a detachment of the choroid and flattening of the anterior chamber 17 days after the operation on the right eye (1952). At that time there was no search for a vitreous hernia, and therefore there is no information as to its presence.

Fourteen days after the operation on the left eye (July, 1953) there was vitreous hernia and flattening of the chamber without choroidal detachment. This, again, confirms the concept that, as the vitreous hernia can appear alone, it is not the result of the choroidal detachment.

The vitreous hernia can produce a choroidal detachment, as it is believed happened in the first eye, but at other times the choroid resists the vitreous traction without becoming detached, as occurred in the second eye.

THE NEW SYNDROME: VITREOUS HERNIA; EMPTYING OF THE ANTERIOR CHAMBER; CHOROIDAL DETACHMENT

I maintain that there exists a direct relation of the elements of this triad.

1. *Internal Vitreous Hernia.*—The well-known vitreous hernia is the fundamental factor in this syndrome.

Duke-Elder † classifies the vitreous prolapses or hernias as external and internal. An external prolapse is that which occurs, for instance, through a perforated scleral wound. An internal prolapse, or hernia, is that in which the vitreous penetrates the anterior chamber.

The internal hernia commonly occurs in three conditions: (1) after an intracapsular cataract extraction; (2) after a discission, and (3) in cases of dislocation or subluxation of the lens.

With regard to the internal vitreous hernia in intracapsular extractions and discissions, Duke-Elder ‡ points out:

> Gentle massage of the globe will always push out a prolapse further, and a sudden trauma, a physical exertion, or even a maximal dilatation of the pupil, is sufficient to increase it, or induce a prolapse when formerly none existed.

Haitz,[7] in a study of traumatic vitreous hernias in the anterior chamber in cases of subluxation of the lens, points out two types: (1) prolapses of lamellar form with rupture of the hyaloid membrane and (2) saccular prolapses in which the hyaloid membrane is intact. According to Haitz, only the last type should bear the name of hernia.

I am completely in agreement with this belief, and when mentioning internal hernias in this work, I refer to the saccular type with intact hyaloid membrane. I believe this difference to be fundamental, for if there is rupture of the hyaloid, as seen in cases of loss of vitreous during the extraction of the lens, the anterior chamber fills with the semifluid vitreous and appears deep. There will probably be no tension on the base, or origin, of the vitreous, as the hyaloid membrane and the vitreous fibrils are broken.

† Duke-Elder,[1] p. 3273.

‡ Duke-Elder,[1] p. 3275.

However, if the hyaloid membrane is intact, the vitreous body will enter the anterior chamber as a whole without mixing with the aqueous, forming a real hernia; then, there will be on one side emptying of the anterior chamber and on the other traction on the origin of the vitreous and a tendency toward a choroidal detachment.

Sallmann § made the interesting remark that when the involution of a choroidal detachment began, the slit lamp showed at a given moment that the hyaloid membrane formed an anterior concavity in the corresponding pupillary area; that is to say, Sallmann foresaw the tension or displacement of the vitreous backward when the choroid became reattached but apparently did not assume that the vitreous was of importance in the genesis of the detachment.

As a demonstration of the slight pathological importance generally given heretofore to the herniation of the vitreous into the anterior chamber, I quote from Kirby [11]:

> The effects of vitreous surging in and out through the pupil after uneventful intracapsular extraction and the protrusion of vitreous into the anterior chamber are interesting. Conditions found after operation vary from a flat vitreous face posterior to the pupil to a mound or a mushroom-like protrusion through the round pupil or to a massive protrusion, particularly through the coloboma, created by a complete iridectomy. If the vitreous is separated by aqueous from the cornea and the limbus incision, it does no harm and may surge back and forth through the pupil with the movement of the eye without causing any damage. The movements of the vitreous as described do not lead to detachment of the retina or to other complications. . . . The altered position of the vitreous does not of itself produce pathology.

Berliner [12] admits a certain significance to the vitreous hernia in the anterior chamber when stating that "it may be a factor in the causation of delayed restoration of the anterior chamber, distortion of the pupil, anterior peripheral synechiae and consequent secondary glaucoma."

I ascribe fundamental importance to the vitreous hernia in the occurrence of the syndrome under study.

In a correct pathological evaluation of any given vitreous hernia, a difference of at least two grades should be considered, even though all the intermediate grades exist. The incomplete hernia shown in Figure 1 *B* is of no great consequence provided that it continues in that state. The complete hernia which is in contact with Descemet's membrane (Fig. 1 *C*), constituting a definite protrusion of the vitreous body in the anterior chamber, produces the emptying of the anterior chamber, and sometimes detachment of the choroid.

With regard to the pathogenesis, I believe that, beside the factors already discussed which assist in the herniation of the vitreous into the anterior chamber, such as fits of coughing, muscular effort, and dilatation of the pupil, a fundamental factor is the quality of the herniatable material, that is, of the vitreous itself. The consistency and volume of the vitreous body are of great importance. Thus, a turgescent or voluminous vitreous will easily herniate. On the other hand, a fluid or shrunken vitreous will probably not herniate even if the patient has violent

§ References 8 to 10. I know of Sallmann's work only through his comments (References 9 and 10).

fits of coughing and a mydriatic pupil. This assumption would explain the relatively low percentage of vitreous hernia following cataract surgery, as the vitreous body commonly suffers senile degeneration.

2. *Emptying of the Anterior Chamber.*—The flattening of the anterior chamber following cataract surgery, as has been shown in the present cases, can be caused solely by the internal vitreous hernia, without any leak of the wound or choroidal detachment. This statement, of course, does not mean that I deny that the leakage of aqueous through the wound is one of the frequent causes of emptying of the anterior chamber.

I do believe, however, that with the multiple corneoscleral sutures employed in modern techniques, the loss of aqueous through the wound is increasingly less frequent and that in most cases of flattening of the chamber, especially when of late appearance, the cause is an internal vitreous hernia.

3. *Choroidal Detachment.*—This is the third element of the triad, and the most changeable.

I hold that the choroidal detachment is caused by the traction that the vitreous, prolapsed into the anterior chamber, exerts on its base, or origin, in front of the ora serrata (Fig. 3). For transmission of this tension it is necessary that the hyaloid membrane and the vitreous fibrils remain unbroken. It is also possible at other times that, owing to greater elasticity of hyaloid and fibrils, less traction is transmitted and the choroid remains attached.

Nor do I assume that the only cause of choroidal detachment is the internal vitreous hernia. A scleral trauma in a healthy eye, for example, can produce a subchoroidal hematoma, with detachment of the choroid. Choroidal detachments in antiglaucoma operations are well known, when the lens is in place and there is no hernia of the vitreous. I wish only to insist that in intracapsular cataract extractions the most frequent cause of choroidal detachment is the internal vitreous hernia.

I have already referred to the clinically important choroidal detachments appearing some days after operation. The operative detachments which frequently occur at or immediately after operation, and which are not generally given clinical importance, owing to their rapid regression, could also be due to the traction of the vitreous at the level of its base, or origin. Undoubtedly, the eye recently operated on shows a condition similar to that appearing in Figure 1 *C*. The space left by the lens and the abolition of the anterior chamber would permit the vitreous body to slide forward, carrying the choroid with it. In this case there is no true hernia, but a displacement forward of the vitreous en bloc. Furthermore, the order of the elements forming the triad has been reversed, as the first event is now the loss of the aqueous and flattening of the anterior chamber and the second, the displacement of the vitreous forward with traction on the choroid. In cases in which there is leakage of aqueous through the wound in the postoperative period this same situation would be produced.

I recently read an interesting paper by Irvine [13] describing a new vitreous syndrome following cataract surgery, characterized by the late rupture of the hyaloid membrane in the pupillary area some weeks or months after the intracapsular

extraction. This author, on describing the base, or origin, of the vitreous of the anatomists in 12 human eyes of adults between the ages of 50 and 70, gives the following description, even though not noting or mentioning choroidal detachment:

> The vitreous structure, at the ciliary body, appears thick and membranous and can be grasped with a forceps without breaking it. Traction on the vitreous, or indenting it at this site, causes an obvious pull on the surrounding ciliary processes and ora.
>
> When a needle, attached to a syringe, is inserted into the vitreous and the plunger is withdrawn, there is a definite pull on the ciliary body no matter where the needle is placed or in what direction the opening of the needle is pointed. Friedenwald demonstrated this effect and I confirmed it on several of these eyes.
>
> When the vitreous is removed from the eye, the base, if pressed between the fingers, has a slippery but definite rubbery consistency, and there is no question about there being a rim of firm resilient tissue in this region.

On the basis of this description, I have carried out the following experiment on two fresh cadaver eyes: The first was an eye which had recently been used as donor for a corneal graft, and the second, the eye of an old man, had been enucleated post mortem to obtain the photographs shown in Figures 4 to 9.

A considerable slice of cornea was excised with knife and scissors, leaving an opening wide enough to permit withdrawal of the lens. A total, ample iridectomy was done. The lens was removed with vectis, without loss of vitreous. Then I cut the eye into two parts with tenotomy scissors, beginning with the limbus and extending the incision backward, endeavoring to keep the two halves of the eye together and to avoid as far as possible the loss of vitreous. When the eye was carefully opened and the hemispheres were placed with cut surfaces up on the table, both halves contained a good amount of vitreous. In spite of this procedure of completely opening the eye, I was surprised by the small amount of vitreous which was lost.

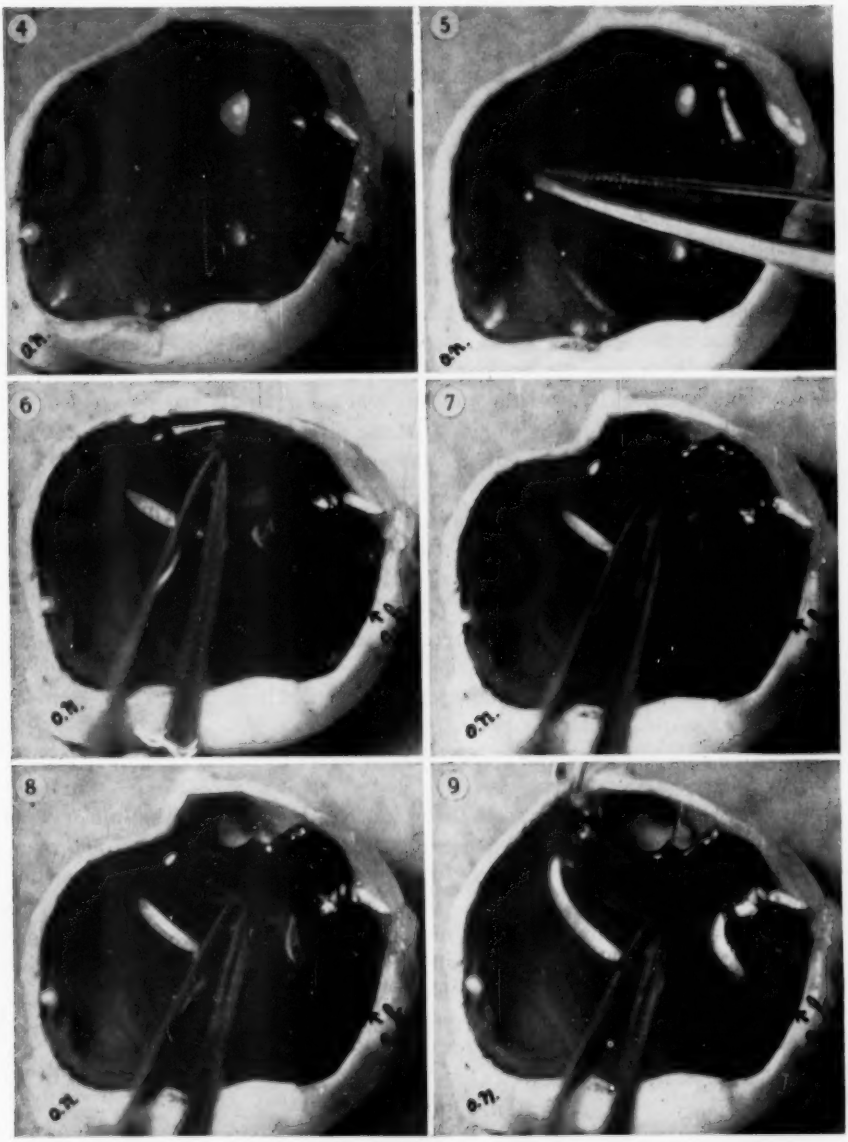
With the eye opened, the choroid continued to adhere to the sclera over its entire surface (Fig. 4). I tried to grasp the vitreous with dissecting forceps behind the equator, near the choroid, and encountered a fluid consistency, causing the forceps to slip, but at times allowing a moderately good hold without visible traction on the neighboring choroid (Fig. 5). On the other hand, at the site of its base, or origin, the vitreous was easily grasped with the dissecting forceps, and its firm consistency allowed a good hold. The traction of the vitreous at this level was clearly transmitted to the uvea, and when the traction was increased, the vitreous was not broken, as might be expected, but the choroid began to detach from the sclera backward from its adhesion to the vitreous base (Figs. 6 to 9).

This anatomical experiment, therefore, exactly reproduced a typical choroidal detachment, such as is seen after cataract surgery. The relatively intense traction which must be exercised with the forceps to detach the choroid explains the inconstancy of the choroidal detachment within the syndrome.

PRACTICAL DEDUCTIONS

Certain important practical applications can be made from the identification of vitreous hernia as the cause of emptying of the chamber and of choroidal detachment.

The first is to avoid the instillation of mydriatics in the postoperative period of intracapsular cataract extraction. If it is desired alternately to dilate and to



Figs. 4 to 9.—Here, *o.n.* indicates the optic nerve, and *c.b.*, the ciliary body (darker color, seen through the vitreous).

In Figure 4 the shining spherules indicate the surface of the vitreous. In Figure 8, note the bending of the sclera at the limit of the detachment, due to stronger adherence of the choroid at this point. In Figure 9 it can be seen that the sclera had to be grasped with a forceps to permit further detachment. In spite of the stronger pull, the vitreous base did not rupture.

contract the pupil, I should advise the use of a mydriatic of short-lasting action, such as eucatropine. After the mydriasis is obtained, it can be neutralized with pilocarpine.

It is especially important that no mydriatics be instilled when the patient is allowed up, and it would probably be convenient to use miotics systematically during this period.

Should the patient cough or vomit, the pupil must be maintained in miosis to allow the iris to act as a truss retaining the vitreous in the posterior chamber, in spite of the increase of the intravitreous pressure produced.

When the vitreous tends to protrude in the anterior chamber during the operation, miotics should be used systematically in the postoperative period.

I believe that sterile air should be injected in the anterior chamber at the end of the intracapsular operation, even more especially when the patient coughs or is restless, in order to push the vitreous body backward while the aqueous re-forms. The bubble should not be too large, in order that air glaucoma may be avoided.

I should advise the use of miotics and rest in bed with the patient in dorsal decubitus as treatment of the vitreous hernia once it appears, with or without choroidal detachment, so that gravity may cooperate in reducing the hernia in the posterior chamber. Only in extreme cases should air be injected in the anterior chamber as a therapeutic measure, as was done in Case 2.

SUMMARY

Four illustrative cases and anatomical experiments have shown that vitreous hernia in the anterior chamber (without rupture of the hyaloid membrane) is a frequent cause of emptying of the anterior chamber and detachment of the choroid following intracapsular cataract extraction.

The emptying of the anterior chamber is due to the expulsion of aqueous humor (through its normal drainage channels) and displacement of the iris forward, produced by the vitreous hernia, without leakage in the operative wound. The detachment of the choroid, which is not of constant occurrence, is due to the traction of the vitreous at the level of its base, or origin, immediately in front of the ora serrata.

Provided that the vitreous body is turgescent, and not shrunken, its herniation in the anterior chamber is produced by an increase of intravitreous pressure (coughing, vomiting, physical exertion) and dilatation of the pupil.

Certain practical deductions concerning prophylaxis and treatment of these complications are made.

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FIRST INTERNATIONAL CONGRESS OF OPHTHALMOLOGY AND CONTEMPORARY STATE OF OPHTHALMOLOGY IN AMERICA

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IN SEPTEMBER of this year the International Congress of Ophthalmology will hold its 17th meeting in Montreal and New York. It was 97 years ago—Sept. 13-16, 1857—that this body met for the first time in Brussels, Belgium. This city was then the home of the first exclusively ophthalmological journal ever published, *Annales d'oculistique*. It seems somehow fitting that the editors of the first journal of ophthalmology should have been the originators and organizers of the first International Ophthalmological Congress and that Brussels should have been the meeting place. It is generally agreed that this meeting was the first international medical congress of any sort.

The January, 1857, issue of the *Annales* carried the first public announcement of the proposed Congress. To supplement the appeal, the journal's editors, in conjunction with the Belgian diplomatic corps, circularized doctors throughout the western world. In the United States the Belgian chargé d'affairés extended the invitations. The response was extremely satisfactory. The "Proceedings" of the Congress, published the following year, lists as participants 31 countries and states. Among the 250 names on the roster are such men as Donders, Sichel, Arlt, Jaeger, Stellwag, Bowman, Dixon, Mackenzie, and von Graefe. (In the edition of the "Proceedings" I used there is inserted a reproduction of the attendance register. Here are the facsimiles of the signatures of all the great and near-great of 19th century ophthalmology.) No American doctors attended, although three, Samuel D. Gross, Isaac Hays, and Squier Littell, all of Philadelphia, did send communications which were printed in the "Proceedings."

The organization committee, composed entirely of Belgian physicians, attempted to give the meeting a universal appeal and international quality by placing on the program five discussion questions which were posed by doctors from countries other than Belgium. The two further questions, although proposed by the committee, had a worldwide significance. The order was as follows: (1) the transmission, treatment, and prevention of military ophthalmia (trachoma); (2) the value of the recently invented ophthalmoscope as a diagnostic aid; (3) the mechanisms of accommodation; (4) the classification of ophthalmias and their treatment; (5) the possible nonsurgical treatment of certain forms of cataract; (6) the use of palpebral occlusion in ocular therapeutics, and (7) the usefulness and nature of

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special eye hospitals. In addition, it was hoped that the delegates would report on the general state of ophthalmology of their native countries. This was indeed an ambitious program.

The seven questions did not receive equal attention from the delegates. The same uneven treatment was reflected in the written reports from the various countries. More was said and written about Question No. 1, that of military ophthalmia, than about any other. This is not surprising when it is remembered that this trachoma had been the scourge of the armies of Europe for more than a half a century.

Much has been made of the role the ophthalmoscope played in shaping the early lines of the medical specialty of ophthalmology; little has been said of the role trachoma played. This disease, more than any other recorded factor, was instrumental in separating reputable physicians of the first decade of the 19th century from the general medical field and in causing them to specialize in treating one anatomical area, one disease. How often this move was made voluntarily is difficult to say. In many instances it was done at the order of the ruler, because military ophthalmia had struck at the very bulwark of national existence, the army. No general staff could plan a campaign, provide for the national defense, or levy troops when it knew that in a matter of weeks the barracks and camps would be filled with blinded and suffering soldiers. So it was at the order of the general staffs of Europe that, first, army surgeons and, later, private practitioners were assigned the task of solving the problem in some fashion. Because these doctors devoted all of their time and energy to one problem, they became specialists, became members of the small band of ophthalmologists already in existence.

The combination of the medical mind and the military mind did not produce therapeutic miracles. In some instances it had exactly the opposite effect.

One of the best-chronicled medical blunders in history grew out of this ill-assorted team. The place was Belgium; the actors were the Belgian Sanitary Staff; the victims were the people of Belgium. In 1834, when the tide of Napoleon's armies had receded into memory, the Belgian army took a census of its veterans and found 4,000 men totally blind from military ophthalmia and 10,000 partially blind. The chief of the Belgian Sanitary Staff was certain that military ophthalmia was not contagious; rather, the cause of its prevalence in the army was the new, unhealthy uniform worn by the infantry soldiers. The shakos exerted too much pressure on the soldiers' heads. Order: Off with the shakos. The white tunics reflected too much light in the soldiers' eyes. Order: Change the color of the tunics. The cravats were too tight around the soldiers' necks. Order: Loosen the cravats. All orders were carried out with characteristic military alacrity, but to the amazement of the chief of the Sanitary Staff, the virulence of the ophthalmia did not abate.

The General Staff lost patience with the Sanitary Staff and, acting upon what it thought was good advice, took matters into its own hands. With one stroke of the pen the Belgian army was rid of trachoma. The method was a simple one: Discharge all soldiers with trachomatous eyes. There were over 4,000 such unfortunates who carried into the cities and towns the unknown virus of trachoma. In a matter of weeks the civilian population was in the grip of the worst epidemic it had ever known. This reached its peak in 1836. What had been the problem of the military surgeon became now the problem of every doctor in Belgium.

There was to be no overnight conquest of the enemy. On the eve of the International Congress, 1857, Belgian doctors were still grappling with the problem. Throughout all of Europe, North Africa, and Asia Minor, in every country, a similar battle was being waged, for military ophthalmia was the No. 1 military and public health problem. It was the one disease with which every doctor had experience, the one subject he had in common with the medical community. Everyone had something to say on the subject, and the Ophthalmic Congress was the perfect place to say it.

The clinical pictures painted by the various delegates were hideously similar. However, there was no general agreement on the question of contagion, etiology, and therapy. This lack of agreement must have been a great disappointment to the members of the organization committee of the Congress, who had held sanguine hopes about finding a solution to the problem.

What contribution did America make to the Congress and its discussions?

Although four names appear on the list of Congress members, no American crossed the Atlantic to attend the meetings. Gross, Littell, and Hays submitted papers to be printed in the "Proceedings"; Dr. Lazarus, of Washington, D. C., made no contribution. The three papers were all that America gave to the first Ophthalmic Congress.

The smallness of the contribution may be explained on the ground that America was not ready for medical specialization, particularly in the field of ophthalmology. Even the words "ophthalmology," "ophthalmologist," and "ophthalmic" were new to the language. The medical community was suspicious of anyone who declared himself an eye specialist. It was a matter of pride with American doctors that they could treat any area of the body, any disease. They had to keep themselves abreast of every advance in medicine and were generally successful.

However, a solid groundwork was being laid for specialization in ophthalmology. There were conscientious men who were devoting a large part of their time to the study and treatment of diseases of the eye; they were writing of their experiences; they were teaching younger men, and there were hospitals dedicated to the care of the eye. Gross, Littell, and Hays were members of this group. The three papers they sent to the Congress were excellent products of *l'ophthalmologie en Amerique* in the mid-19th Century.

The prolific Samuel Gross gave the best and most complete report. Successful as a writer, as a teacher, as a research worker, and as a surgeon, practitioner, and pathologist, Samuel David Gross (1805-1884) was almost wholly a product of American medical education and self-training. He began at the age of 17 as a reader in the office of a small-town physician. A short time later he went to Philadelphia and entered the newly founded Jefferson Medical College. Here he came under the influence of Dr. George McClellan, one of Philadelphia's early ophthalmologists. He completed his terms of lectures at Jefferson and wrote a doctoral thesis on the nature and treatment of cataract. He decided to commence his practice of medicine in Philadelphia. During this early period of his career he augmented his meager professional earnings by translating French and German medical textbooks into English and by writing a textbook of his own. In 18 months' time he had translated and written nearly 1,500 pages octavo. Leaving Philadelphia, he went to his native Easton, Pa., for a short time. From there he went to Cincinnati

for a six-year stay as teacher and practitioner. Then an opportunity came to go to Louisville Medical Institute as professor of surgery. There he stayed for 16 years. In 1856 he returned to Philadelphia and took the chair of surgery at his alma mater, Jefferson Medical College. Twenty-six years later he resigned. Forty-nine years of his life was spent as a teacher of medicine and surgery.

Gross was highly regarded by his contemporaries. He wrote the first systematic textbook of pathological anatomy in the English language. Virchow gave great praise to this work. In 1859, his "System of Surgery" was published. He was honored by degrees from Oxford and Cambridge Universities. After his death the Congress of the United States appropriated money for the erection of a statue of him. Yet in spite of his forward-looking nature and his many research attempts, he was quite typical of his time and the medicine of his day. He was on the wrong side of the line that falls somewhere in the 19th Century—the line that marks the beginning of modern medicine. His medicine, and it was the medicine of Hays and Littell as well, was the medicine of the leech, the seton, the blister, and the cup. His prescriptions were for calomel, jalap, Dover's powder, metallic salts, and derivatives of the poppy. Noxious effluvium played a large part in the etiology of the diseases he treated. In spite of this, he did advance medicine and medical education, and he was more than worthy of every honor he garnered.

Gross was well qualified to write a report on ophthalmology in America. He knew the subject as well as, if not better than, most doctors of his time. He knew America, for his professional and teaching activities had taken him into every area of the country east of the Mississippi. Always a man of method, he considered each question on the program of the Congress and answered it fully and to the point.

In his paper he told the Ophthalmic Congress that the American Army was free of military ophthalmia and as such could not be a source of infection. However, "granular conjunctivitis" was spread throughout all the states, in the rural and the urban areas alike. It was endemic in the states drained by the Ohio and Mississippi rivers. Gross thought that, possibly, this variety of ophthalmia had a common origin with the malarias, agues, and neuralgias from which the people of this area suffered.

He drew the following clinical picture: The inflammation would develop rapidly, often overnight. The eyes would become extremely painful and swollen, the conjunctiva very red. There would be a purulent discharge, lacrimation, and photophobia. After two or three days, granulations would appear on the internal surfaces of the lids. Children and women were rarely afflicted, the disease being commonest among men in the age group of 20 to 60 years. Both eyes were usually affected.

On rare occasions there would be a more intense form of the malady, which often ended in gangrene of the cornea and complete loss of sight. Usually the inflammation was of a chronic nature, lasting for months or years, and bringing on an opacity of the cornea and loss of vision. The bottomlands of Indiana and Illinois knew many cases of complete blindness due to this cause.

Gross had definite proof that the discharge from the inflamed eyes was contagious by contact. He had seen whole families who had used common wash basins and towels infected from an afflicted member. He had witnessed the same thing in boardinghouses and hotels.

He could offer the assembled ophthalmologists no completely satisfactory treatment for "granular conjunctivitis." He had tried scrupulously for a long time to find a means of treatment but had met with disappointment. For several years he had limited his treatment to the excision of the more prominent granulations, scarification of the lids, applications of copper sulfate, and setons. He did not neglect to observe the general health of his patients. If it was poor, he prescribed quinine and iron, light diet, and outdoor exercise. At bedtime 16 to 20 grains of Dover's powder was administered. The latter seemed to lessen the pain and photophobia, as well as the lacrimation. He had no success in using leeches or cupping his patients. The bathing of the temples, forehead, and eyes with hot salt water had given him some success. In various degrees and combinations he had tried Goulard's extract, acetate of lead, and sulfate of alum, but none of these rendered the service copper sulfate did. During the final stages of the inflammation he had employed with success an ointment of red oxide of mercury or nitrate of mercury.

It was his experience that "purulent ophthalmia without granulations" was very rare in the United States. It was sometimes, without apparent cause, in the eyes of newborn infants. After many trials Gross found that this condition yielded to the following therapy:

"a solution of bichloride of mercury, in proportion, for new-born children, of an ⅛ of a grain in a dram of warm water and 7 drams of ordinary water. One injects this solution every two hours, after having first cleaned the lids with warm water. I always use at the same time a small dose of Dover's powder and calomel, ¼ to ⅓ of a grain the first day and ⅛ of a grain the second day, three or four times a day.

The children of the poor of America, Gross said, were prone to suffer from "scrofulous ophthalmia." Sometimes a child from a well-to-do family might also be afflicted. Here Gross treated his young patients with quinine, opium, or tartar emetic. He kept a careful watch on the general state of health. He had no use for any sort of collyrium. If the case were stubborn, he added to the tonics a small quantity of bichloride of mercury, about 1/20th of a grain. Where there was an opacity of the cornea, he found tartar emetic most useful. The largest dose he prescribed was 1/30th of a grain. He considered opium a most important aid because it lessened the photophobia. If the case were stubborn and of long duration, he used a gentle astringent ointment.

He went on to report that the United States was fortunate in that "neuralgic ophthalmia" was rare. Such cases as did exist yielded to doses of quinine administered every six or eight hours.

Concerning cataracts, he said, they were common to all ages and all classes of society, among city dwellers and country people.

At this point in his article, Gross ceases to report on diseases of the eye and turns his attention to ophthalmic practitioners, literature, and hospitals. Not enough attention was paid to the study of ocular conditions in America, he said. True, there were hospitals for the eye in Philadelphia, Boston, New York, and other cities of the eastern seaboard, but inland the people were either neglected or treated by quacks and charlatans. The United States had made only two major contributions to ophthalmic literature: Frick's "Treatise on the Eye" and Littell's "Manual." Gross did not regard Frick's work too highly, stating it was little more than a

résumé of Beer's book. Littell's "Manual" he found excellent. The most widely read textbooks on ophthalmology were those of Lawrence and Mackenzie.

The ophthalmoscope was used here and there by rare practitioners. Gross felt that his friend Elkanah Williams, of Cincinnati, was one of those who made the best use of the new instrument. Dr. Hewson, of Philadelphia, also used the instrument frequently in his practice.

Gross closed his article by repeating that after diligent inquiry he found that ophthalmia in any form had never been known, either endemically or epidemically, in the United States Army. Not in any of its wars or campaigns had its soldiers been afflicted.

The second American contributor, Squier Littell (1803-1886) of all Philadelphia doctors of his time most nearly approached being an ophthalmologist in the modern sense of the word. He had been a member of the staff of Wills Hospital for a number of years; a large part of his practice was devoted to diseases of the eye, and his principal medical writings were on ophthalmology. A gentle, conscientious, religious man, his life was marked by sorrows and disappointments, which deepened his naturally melancholy nature. His parents died when he was a boy. His desire to be a teacher of medicine was curtailed by a speech impediment. His wife, whom he loved deeply, died at the birth of their second child. Much of his energy was turned to the field of religion and literature. At one time he wrote twelve poetic versions of the medieval hymn *Dies Irae*. Near the end of his life he developed choroiditis, and the last three years of his life were spent in near-helplessness.

His most outstanding contribution to ophthalmology was his "Manual on Diseases of the Eye," an excellent, original monograph, which was described as "embracing all that is valuable and necessary to the student, within the compass of two hundred and fifty small pages. It is replete with information, yet so terse in style, and compressed in bulk as at once to entice and repay perusal."

Littell did not attempt to write on the state of ophthalmology in America; rather, he confined his report to his native city of Philadelphia and to his own hospital, Wills. Through him, the Congress learned the history of Wills Hospital, of its benefactor, its finances, organization, patients, and construction. He reported that many cases of "granular conjunctivitis" were treated at Wills. The method of treatment decided upon by the staff was not too different from that advocated by Gross: bleeding, purging, and diet, with chief reliance placed on silver nitrate. In cases that were mild, a solution of 4, 8, or 10 grains was dropped upon the eye or applied to the conjunctiva by means of a camel's hair pencil, once or twice a day. When the inflammation was greater, a solution of 15 to 20 grains was used. It was recommended that the eyes be bathed frequently with warm water or a weak solution of bichloride of mercury. No towel or sponge that had come in contact with the discharge was to be reused before being disinfected. Pain was controlled by opium and laudanum. The patients' rooms were well ventilated, and whenever possible the patients received exercise in the open air. The same treatment was recommended for gonorrheal ophthalmia.

The paper by Isaac Hays (1796-1879) was the shortest contribution of the three coming from America. It was less than a page and a half in length and was devoted

to redescribing a knife he had devised for the discission of hard cataracts. The knife combined the advantages of a knife and a needle and was for some time popular with American ophthalmic surgeons.

Hays's contribution to the Congress "Proceedings" may have been small, but his contribution to medicine, medical literature, and ophthalmology were many and large. Fifty-two years of his professional life were spent in editing American medical journals and textbooks, the last two being on ophthalmology. The pages of the journals he edited were for many years the only certain and continuous source of ophthalmic literature available in America. To him goes the honor of observing and reporting for the first time a case of noncongenital color blindness. For 20 years he was on the staff of Wills Hospital, and, with Littell and Parrish, shaped the early policies of that institution.

With these written contributions from America, and with others from all over the western world and the thousands of words from the minutes of the discussions to guide them, the organization committee of the First International Ophthalmological Congress framed answers to the seven questions posed at the outset of the meetings.

They concluded that military ophthalmia was contagious on contact, that certain localities and the nature of the air favored the development of the malady. They could not recommend one course of treatment over another, feeling that military ophthalmia was too variable an entity to bow to any one therapeutic regime. To prevent the appearance and the spread of trachoma, they offered a detailed program designed for use in barracks and military hospitals. In brief, this program was one of complete isolation of the patients, scrupulous cleanliness, careful diet, and outdoor exercise.

For the ophthalmoscope they had only words of praise: What was once hidden could now be seen; what was once obscure was now precise.

They favored the recently advanced theory of Helmholtz concerning the mechanisms of accommodation.

They did not attempt to classify the ophthalmias.

Cataracts, it was felt, could not be cured; surgery was the only answer, even though certain types of cataracts had responded to an unspecified treatment.

They generally favored the use of palpebral occlusion in cases of ulcers and perforations of the cornea, "hernia" of the iris, and staphylomas, and after cataract operations when an artificial pupil had been formed.

In reporting on special eye hospitals, they expressed the belief that such institutions should have the same facilities as other hospitals, although greater care should be taken in their design. The building should have an east-west exposure; the walls should be painted in neutral tints of gray, green, or blue. Special wards should be provided for contagious cases. The operating room should have a north window. If the hospital was to be a teaching hospital, an amphitheater for instruction and demonstrations should be provided. They urged the establishment of a special chair in ophthalmology at each medical school.

The last paper read, the last discussion ended, the word-weary delegates sat down to a banquet. Toasts were drunk; farewell speeches were made, and an atmosphere of geniality spread over the delegates. At 10 o'clock on Wednesday evening, Sept. 16, 1857, the First International Congress of Ophthalmology closed.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

BEHCET'S DISEASE

THIS case is reported because of its rarity, the patient being the only native-born American female reported to date with Behcet's disease. Most intriguing also is the appearance of so typical a case of this rare condition, most prevalent in the Eastern Mediterranean region, in so isolated a geographical area in a patient who had not traveled abroad.

REPORT OF CASE

G. H., aged 20, a woman telephone operator of English ancestry, was led into my office on Aug. 5, 1949, with a complaint that "a cold had settled in her eyes" about two weeks before and her vision was failing. Further questioning revealed that she had had four such attacks in the previous six months and had had two pairs of glasses prescribed, but had received no other treatment or diagnostic procedures.

Vision was counting fingers at 1 ft. (30 cm.) O. D. and at 5 ft. O. S. and could not be improved with lenses. The eyes were free from conjunctival or limbal injection; the corneae were clear; intraocular tension was normal, and there was a slight flare in both anterior chambers. The vitreous chambers were too clouded for observation of fundus details, but a very definite swelling of both discs with vague chorioretinal lesions in both posterior segments could be seen. A general physical examination, including urinalysis, blood serology tests, chest x-ray, pelvic examination, and dental consultation, was negative (save for two questionable teeth, which were removed), as was the E. N. T. consultation. Symptomatic treatment apparently effected a cure, for in about 10 days vision was up to 20/200 O. U. and the vitreous cavities had cleared enough to permit a good view of the fundi, which were involved around the discs and maculae, with nonspecific deposits of pigment and exudate.

The left eye had a recurrence on Sept. 16, 1949, and, since this bout was seen early, the characteristic hypopyon was in evidence; this was present at the beginning of most of the subsequent recurrences. Tests were negative for tuberculosis and brucellosis at this time; but in January, four recurrences later, another tuberculin test gave a 4 + reaction, and several months of therapy with graduated doses of old tuberculin U. S. P. followed, with no apparent benefit.

Deep, necrotic aphthous ulcers on the tongue and in the mouth were first noted in March, 1950, and from that time became a part of each succeeding recurrence; if anything, they caused more discomfort than the ocular condition. This is saying a great deal, because the left eye had developed a secondary glaucoma which did not respond to any medical management and was blind. I and two consultants recommended enucleation of this eye, but the patient would not consent to this procedure; in the faint hope of reducing the pressure and relieving her pain, I did an iridectomy and extraction of the swollen opaque lens on April 10. The operation apparently succeeded in these respects, but an attack of uveitis in the right eye, which still had about 10/200 vision and had been quiet for five months, caused me to insist on an enucleation of the left eye within a month. The enucleation was done under general anesthesia.

During the induction of the anesthesia the patient flounced about a bit, and, quite by accident, one of the operating-room nurses discovered several large necrotic ulcers around the patient's vulva. These ulcers perforated the labia majora. A gynecologist, who was called in from a

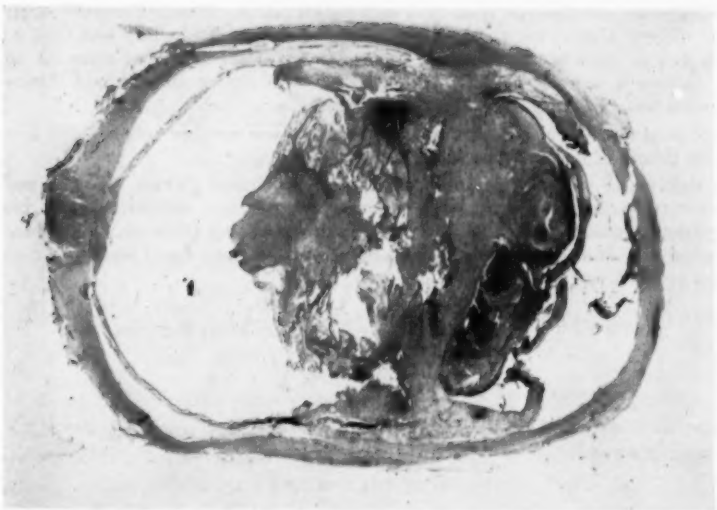

Fig. 1.—Section of globe; × 6.6. This organized inflammatory mass is predominantly lymphocytic.

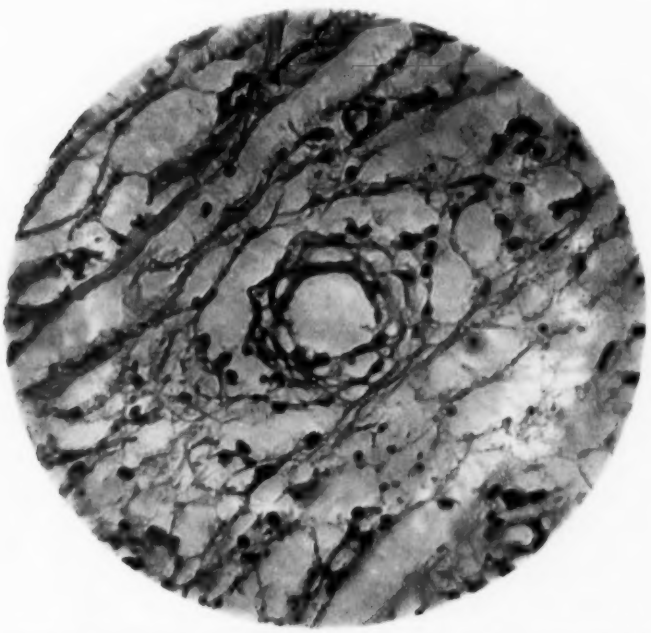

Fig. 2.—High-power view showing the round-cell perivascular infiltration that is probably the fundamental lesion in Behcet's disease.

neighboring room, stated he had never seen such lesions before. After the patient had recovered from her surgery, I asked her about these lesions, and she stated that they had come on about the same time as those in the mouth but she feared that if she mentioned them she might be thought to have a venereal disease. A consultation with a dermatologist was obtained, and his diagnosis was "aphthous ulcers"; scrapings yielded no growth.

A superficial thrombophlebitis of the calves and ankles was noted on July 30, 1951, completing the clinical picture of Behcet's disease.

This unfortunate young woman, in the course of her disease (which still continues), had antihistaminics, smallpox vaccinations, salicylates, fever therapy, corticotropin and cortisone, and the various antibiotics, all of which gave the illusion of helping (at first), by the spontaneous regression of each episode. An attempted allergic work-up was abandoned because of the strong, sometimes pustular, reaction evoked by each test.

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Annual Reviews

PHARMACOLOGY AND TOXICOLOGY

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REFERENCE is made to previous reviews of this topic.* Many current reports which merely corroborate the conclusions presented in previous reviews have not been included here because of space limitations. Certain topics, not covered in last year's review, are included, publications of the past two years being drawn upon.

RADIOACTIVE ISOTOPES

The development of the nuclear reactor has made feasible the quantity production of a number of radioisotopes, many of which have proved valuable as diagnostic and therapeutic agents. The disintegration of radioactive nuclei produces two types of clinically useful energy, the beta and the gamma rays. The beta rays penetrate only a few millimeters of tissue and hence are equivalent to the softer x-rays, or Grenz rays.[3] The gamma rays are more penetrating, resembling x-rays of higher energy. Otherwise, the biologic effects of beta and gamma rays are similar. Such factors as the type of radiation produced, its energy, the half-life of the isotope, and the metabolic role of the naturally occurring substance will determine the selection of the isotope to be used in a given clinical situation. For the purposes of discussion, distinction will be made between those isotopes which deliver radiation externally, as by teletherapy or contact, and those which are administered systemically.

External application of radiations from radioactive isotopes is limited largely to therapeutic usage. Such use of beta ray therapy is confined to the treatment of superficial lesions. The common sources of beta rays are radioactive strontium (Sr^{90}), a pure beta-ray emitter; radon, and radium D and E. Radioactive phosphorus (P^{32}), also a pure beta emitter, has had little use in superficial therapy, although it has been suggested for the treatment of patients with multiple basal-cell carcinoma.[4] However, because of the short half-life, its use in office practice is inconvenient. About the eye Sr^{90}, radon, and radium D and E have been used, various applicators having been devised.† Successful treatment of a variety of superficial lesions, including tumors, pterygia, and corneal vascularizations, has been reported. An excellent review of the uses, hazards, and limitations of beta radiation in ocular therapeutics is available.[9] The necessity for accurate control of the dose is emphasized. Focal scleral necrosis has been reported following irradiation with a relatively modest dose (1,500 rep) delivered from a Sr^{90} applicator.[10] Moreover, the possibility that beta rays may be injurious to deeper structures should be borne in mind. The application of some 5,000 rep from Sr^{90} to the limbal areas of rabbits was shown to induce cataracts, even though a maximum of only 15% of this radiant energy was delivered to the lens equator.[11]

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* References 1 and 2.

† References 5 through 8.

A discussion of the use of various gamma emitters for therapy has recently appeared.[12] Those radioisotopes which can be produced in the nuclear reactor are relatively cheap sources of gamma radiation as compared with radium. That most frequently used as a substitute for radium or radon in interstitial and intercavitatary therapy is radioactive cobalt (Co^{60}).‡ Co^{60} is also used as a source of gamma radiation for teletherapy units. Another suggested use of gamma radiation is the sterilization of pharmaceuticals in finished package form.[17]

The radioisotopes are administered systemically for both diagnostic and therapeutic purposes. As a diagnostic agent, an isotopically marked compound which remains within the confines of the vascular tree provides a ready tool for the detection of a relatively vascular mass. The isotope most frequently used for this purpose has been radioactive iodine (I^{131}), a beta and gamma emitter. Generally, human serum albumin or fluorescein is iodinated with this isotope, the preparation of such derivatives being quite simple. When one of these isotopes is injected into the blood stream, a relative increase in radioactivity can be detected over a highly vascular area, even though deep-seated. This technique has been of particular value in the localization of intracranial neoplasms.§ An unsuccessful attempt similarly to employ radioactive diiodofluorescein for the diagnosis of intraocular tumors has been reported.[21] The gamma rays of I^{131} are highly penetrating, and the employment of these agents for the detection of ocular tumors presents certain technical difficulties.

The second diagnostic use of these agents depends upon their preferential uptake by the individual cell and varies, therefore, with the substance and the metabolic activity of the cell. Thus, the thyroid gland takes up iodine, and the accumulation of injected I^{131} by the gland provides an accurate measure of the thyroid status of the subject. Similar use of P^{32} depends upon the incorporation of inorganic phosphate containing P^{32} into the organic phosphate fraction of cells. Those cells which are most active biologically, and therefore have the most rapid turnover of phosphorus, will show the highest uptake of injected radioisotope. Malignant cells fall in this classification. Since P^{32} is a beta emitter only, its use for the detection of malignant growth is largely limited to superficial lesions, although the location of brain tumors by using a probe counter at operation has been described.[22]

The use of P^{32} for the detection of intraocular tumors has proved valuable. For this purpose a quantity of P^{32} (sufficiently small to exert no depressing effect on the bone marrow) is injected intravenously. After varying time intervals the radioactivity of the region in question is measured, using an end-window counting tube of proper geometry. Control readings are taken from an anatomically comparable site in the same or in the opposite eye. It is reasonable to suppose that a vascular mass of any description, such as a muscle,[23] inflammatory lesion, or vascular malignant tumor, would show early high activity. This may present a handicap, since differentiation of a tumor from an inflammatory process may be required. Nonetheless, rapid uptake of radioactivity has been shown to be indicative of malignant lesions.[24] Thus, ready uptake of P^{32} during even the first few minutes may represent more than just a vascular mass. Probably each case must be considered individually, and radioactivity measurements for two hours or longer may

‡References 13 through 16.

§ References 18 through 20.

be necessary for final evaluation. Other diagnostic aids have been mentioned, such as the variation in activity with the distance from the scleral surface.[23] With the present equipment, detection of tumors in the posterior segment of the eye is difficult, if not impossible. In spite of the shortcomings listed, the use of P^{32} for the detection of intraocular malignant tumors, such as melanomas and retinoblastomas, has been rewarding.|| Additional technical refinements should increase the value of the procedure.

The therapeutic use of the radioactive isotopes by either parenteral or oral administration also depends upon their selective uptake by a particular type of cell. Thus, radioactive iodine is valuable in the treatment of thyrotoxicosis ¶ and, to a certain extent, in thyroid cancer.[30] P^{32} has proved of particular benefit in the treatment of polycythæmia rubra vera and certain chronic leukemias.# Radioactive gold, particularly in colloidal suspension, has been useful in the palliation of symptoms in metastases to the abdominal and pleural cavities, reducing the peritoneal or pleural effusions.* The regional lymph nodes selectively assimilate these particles, especially when they are silver-coated.[37]

Finally, mention should be made of various agents which exhibit a protective effect against radiation damage. These include sodium nitrite,[38] certain flavonoids, such as rutin,† and such sulfhydryl-containing compounds as cysteine, glutathione, and cysteinamine (β-mercaptoethylamine).‡ Protection is afforded not only against the general manifestations and lethality of total body irradiation, but also against local irradiation. Thus, the sulfhydryl compounds minimize radiation damage to the cornea [49] and the lens.[50] However, these agents do not shield against the mutagenic effects of ionizing radiations.§ The sulfhydryl compounds probably prevent the oxidation of some key sulfhydryl group or groups, but other explanations for their beneficial effect are feasible. Interestingly enough, cysteinamine reduces the toxicity of high oxygen tensions (six atmospheres) in experimental animals.[54]

ANTIMALIGNANT AGENTS

The antimalignant agents in commonest use fall into two groups, the folic acid antagonists and the nitrogen mustard or nitrogen mustard-like agents. The folic acid antagonists appear to act as antimetabolites; i. e., they are chemically similar to and compete with folic acid but are incapable of exerting the latter's metabolic function.[55] Thus, both the therapeutic and the toxic effects of the folic acid antagonists are probably due to a folic acid deficiency. Aminopterin has been one of the most widely used of this group of drugs, usually being employed in the treatment of leukemia.||

The nitrogen mustards and nitrogen mustard-like drugs comprise the other major group. Their cytotoxicity is due apparently to a cyclic onium (imonium, sulfonium) structure. This readily reacts with many different radicals, e. g., amino and sulfhydryl groups; and as a result the drugs are potent enzyme poisons. Physiologically,

|| References 25 to 27.
¶ References 28 and 29.
# References 31 through 33.
* References 34 through 36.
† References 39 through 41.
‡ References 42 through 48.
§ References 51 through 53.
|| References 56 and 57.

they are most toxic to cellular nuclei, particularly to nuclei of actively proliferating cells, a breakdown of nucleoprotein being one of the manifestations of their action. However, the nitrogen mustards may modify many enzymes and proteins, and their clinical use has not been limited to the treatment of neoplasms.

The nitrogen mustard most frequently employed is methyl-*bis* (β-chloroethyl) amine hydrochloride. Triethylene melamine is the most widely used of that large number of compounds termed nitrogen mustard-like drugs. Triethylene melamine has certain advantages for clinical use, since it can be administered orally and is less toxic than methyl-*bis* (β-chloroethyl) amine. These substances have been most effective in the treatment of neoplasms of the lymphoma group, particularly Hodgkin's disease and the leukemias. The response of other malignant growth has been less dramatic.¶ Equivocal success in the treatment of malignant melanomas with use of another of the nitrogen mustard-like drugs (triethylenephosphoramide) has been reported.# The use of these drugs seems justified in the treatment of malignant tumors that have not responded, or may not be expected to respond, to other therapeutic measures. However, even when most successfully employed, the nitrogen mustards and similar drugs are not curative. Their combined use with x-ray therapy as a primary procedure may have special merit, as suggested by a report of such use in the treatment of retinoblastoma.[73] In this case the clinical benefit was considered to be greater than that which could have been achieved with x-rays alone.

Nitrogen mustard and triethylene melamine have been tried in the treatment of such non-neoplastic diseases as glomerular nephritis, the nephrotic syndrome, acute disseminated lupus erythematosus, rheumatoid arthritis, and asthma, with variable success.* The disturbing side-effects of these drugs include nausea and vomiting, dermatitis, psychosis, and, more serious, a leukopenia and thrombocytopenia which may prove fatal. Acute renal failure from uric acid crystallization, presumably due to the increased excretion of uric acid caused by nucleic acid breakdown, has been reported.[80] For this reason, the concurrent administration of sodium bicarbonate has been recommended. Cysteinamine has been observed to reduce the toxicity of nitrogen mustard to tumor-bearing animals without altering its antimalignant properties.[81]

The treatment of certain skin carcinomas by various topically applied agents continues to be reported. These include zinc chloride [82] and podophyllum resin N. F. While successful use of the latter for the treatment of basal-cell carcinomas has been reported,[83] its value seems doubtful.[84]

VITAMINS

As pharmacologic agents, vitamins are primarily indicated for the treatment of the deficiency state. (Among the causes of avitaminosis should be included the deficiency induced by administration of an antimetabolite. For example, a pyridoxine deficiency can be induced in man by feeding desoxypyridoxine.[85] Whether such a deficiency is ever clinically encountered cannot be stated.) The clinical and experimental manifestations of the various frank avitaminoses are fairly well defined,† and the benefit of vitamin therapy in these instances is clear-cut. (Although the function of many vitamins in cellular metabolism is known and the metabolic dis-

¶ References 58 through 70.
# References 71 and 72.
* References 74 through 79.
† References 86 through 91.

turbance resulting from their absence can be anticipated, the causal relationship of this metabolic disturbance to the clinical manifestation of vitamin deficiencies is generally obscure. One notable exception, of course, is the relationship between vitamin A deficiency and night blindness.) The detection of mild or subclinical deficiency, however, is less certain. Various laboratory tests, such as the measurement of the blood level of the vitamin, and excretion of test doses, have been employed as diagnostic tools.‡ In general, they have not provided an unequivocal answer, and clinical trial of the vitamin, administered in therapeutic dosage, has remained the best diagnostic aid in such conditions.

The use of vitamins has not been limited to the treatment of deficiency states, however. Numerous claims of benefit from vitamin therapy in a variety of clinical conditions annually appear. Generally, massive doses are employed, presumably with the thought that these agents exert a drug action not related to their known role in metabolism, or perhaps with the thought that the known metabolic effects of vitamins can be enhanced beyond the optimal conditions provided by adequate dietary intake. That there is little substance for either conclusion is indicated by the fact that, with the exception of the toxicity induced by vitamins A and D,§ vitamins are tolerated without demonstrable effects in doses up to many hundred times the normal requirement.

Special mention should be made of vitamin B_{12}, recent isolation of which culminated an intensive search for the extrinsic factor of Castle. Cyanocobalamin (crystalline vitamin B_{12}) contains cobalt and a cyanide radical. Replacement of the cyanide group by other radicals gives rise to a series of B_{12} vitamins (the cobalamins).‖ One of these, hydroxocobalamin (vitamin B_{12b}) is present in small concentration in commercially available preparations of vitamin B_{12}.[101] Hydroxocobalamin is not so active against pernicious anemia as cyanocobalamin.[102] It has certain antidotal properties in the cyanide poisoning of experimental animals.[103] The metabolic function of vitamin B_{12} has been intensively studied. An important effect is exerted on amino acid and protein metabolism.¶

Vitamin B_{12} is essential for the maturation of the red cell and has well-documented merit in the treatment of pernicious anemia, producing both a hematologic and a neurologic remission. It is effective via the intramuscular, intravenous, or intranasal route.# When the substance is taken orally by a patient with pernicious anemia or a patient who has had a total gastrectomy, practically all the administered vitamin B_{12} is excreted in the feces. Simultaneous administration of normal gastric juice reduces this excretion to normal levels.* Presumably, the absorption of vitamin B_{12} is enhanced.

Diabetic patients with retinopathy are reported to excrete a significantly greater amount of an intramuscular test dose of vitamin B_{12} than do nondiabetics or diabetics without retinopathy.[115] In the same study it was shown that testosterone decreases the urinary excretion of vitamin B_{12} administered to persons with diabetic retin-

‡ References 92 through 94.

§ References 95 through 98.

‖ References 99 and 100.

¶ References 104 through 106.

References 107 through 111.

* References 112 through 114.

opathy. As mentioned in last year's review, the hydroxycorticosteroids have some as yet unidentified role in the development of diabetic retinopathy and nephropathy. Thus, it is interesting to note that the administration of cortisone to vitamin B_{12}-deficient rats significantly increases the incidence of renal lesions.† Whatever the significance of the observations, it is clear that the administration of vitamin B_{12} and liver extract [116] does not significantly alter the course of diabetic retinopathy.

The stimulating effect of vitamin B_{12} (and the antibiotics) on the growth of certain experimental and domestic animals led to its trial in the nutrition of premature infants; no benefit was observed.[117] The use of vitamin B_{12}, generally in large doses, in trigeminal neuralgia,[118] lupus erythematosus,[119] and other disorders has been suggested. However, in general, its benefit in clinical medicine other than in the treatment of certain megaloblastic anemias remains to be established.

LOCAL ANESTHETICS

The possible mechanisms by which the local anesthetics induce anesthesia have been recently reviewed.[120] Although these drugs reduce the metabolic activity of nerve fibers, this effect does not parallel their anesthetic activity and probably does not account for the local anesthesia these drugs induce. More likely, the local anesthetic agents alter the permeability of the limiting membrane of the nerve and thus influence the rapid exchange of cations which presumably is essential for the propagation of the nerve impulse. With the recognition of certain similarity in structure between the local anesthetics and acetylcholine, an alternative theory suggests that these agents compete with acetylcholine for an enzyme present in the nerve fiber which is involved in the energetics of nerve impulse transmission. A similar competition for a serum esterase is discussed below. The exact role of acetylcholine in the transmission of the nerve impulse, however, is uncertain. In the final analysis, a unified concept of the mechanism of local anesthetic action cannot be given. Indeed, different local anesthetics, such as procaine and tetracaine, do not have the same relative effect on nerve conduction in all sensory fibers.[121]

The local anesthetics have certain atropine-like and antihistaminic action,‡ but these properties appear to be unrelated to their local anesthetic potency. (Conversely, the antihistaminics and certain cholinergic blocking agents have local anesthetic action.) Their antihistaminic action is weak, and, although they have been suggested for the treatment of certain allergic disorders, their effectiveness in this role remains doubtful.[124] It is of interest to note that histamine may partially override the anesthesia induced by procaine.[125] This fact may account in part for the diminished anesthetic potency of these drugs when injected into inflamed tissue, although other factors, such as increased absorption of the agent, are also operative.

Procaine and other local anesthetics, such as tetracaine, are hydrolyzed by an esterase normally present in relatively high concentration in human serum.[126] Acetylcholine and procaine act as competitive inhibitors for this enzyme.[127] Cholinesterase inhibitors, such as physostigmine and neostigmine,[128] also inhibit the hydrolysis of procaine by plasma, probably on a competitive basis as well. It seems likely that

† Becker, B.; Davies, G. M.; Allen, R.; Winter, F., and Friedenwald, J. S.: Role of the Adrenal Cortex and Vitamin B_{12} in Diabetic Retinopathy, presented before the Association for Research in Ophthalmology, New York, June 1, 1953.

‡ References 122 and 123.

serum cholinesterase and serum procaine esterase are very similar, or even identical. However, the cholinesterase inhibitors have an unpredictable effect on procaine toxicity, in some instances reducing the toxic response and increasing it in others.

While there is no fundamental reason for distinguishing between surface and injectable anesthetics,§ such distinction is clinically convenient. Procaine remains the most widely used of the injectable local anesthetics. Its effectiveness is often heightened by the addition of epinephrine. Various modifications of the salt form, as well as alterations in chemical structure, of procaine have been made in an attempt to decrease its toxicity and alter the onset and duration of anesthesia. The ascorbic acid salt is reported to be less toxic and to have greater antihistaminic effect than the hydrochloride of procaine, the anesthetic potency being the same.[130] A mixture of procaine base, procaine hydrochloride, and butyl aminobenzoate N. F. (Butesin) in a polyethylene glycol-propylene glycol vehicle has been marketed as Efocaine, a long-acting (several days) anesthetic agent.‖ In early reports the prolonged anesthesia was attributed to a local precipitation of the procaine base. However, severe neurologic complications following the use of the mixture have been observed,[134] and more recent studies ¶ have indicated that the prolonged anesthetic effect of these agents is not due to the procaine base but is the result of tissue destruction induced by the vehicle, the effect being not unlike that of absolute alcohol.

Each year new local anesthetics are developed as the search continues for the one agent which has all the attributes desired in a local anesthetic, particularly low toxicity, high potency, rapid onset of prolonged anesthesia, and topical effectiveness. Many of the newer agents which have had clinical trial have recently been reviewed.[120] One of the anesthetics most widely studied in recent years has been lidocaine (Xylocaine). This compound produces good surface anesthesia and is said to give more rapid and prolonged anesthesia than procaine on injection.# It is somewhat more toxic than a procaine solution of equal strength. Retrobulbar injection of a 1% solution of lidocaine hydrochloride was found to produce clinical results similar to those obtained with use of a 2% procaine hydrochloride solution with added epinephrine, although the akinesia from lidocaine was less marked.[140] In addition to cocaine, topical anesthetics used in ophthalmologic practice have included such agents as tetracaine. Within the past year, newer topical agents which are said to give more rapid action and to produce less tissue irritation than tetracaine have been reported.*

Procaine hydrochloride, tetracaine, and procaine amide have been tried as analgesics and antipruritics, administration by both the oral and the intravenous route being employed.† Although some success has been reported, their value in this regard has not been striking. Effectiveness of a mixture of procaine hydrochloride and ascorbic acid taken orally for pruritis has been claimed.‡ Finally, procaine hydrochloride and procaine amide hydrochloride are reported to reduce the irritability of the myocardium. They have been employed for this purpose prior to and during

§ References 123 and 129.
‖ References 131 through 133.
¶ References 135 and 136.
# References 129 and 137 to 139.
* References 141 and 142.
† References 143 through 146.
‡ References 147 and 148.

surgery and in the treatment of ventricular tachycardia.§ Procaine amide hydrochloride has found more widespread use, since it is less toxic than procaine hydrochloride. However, fatal ventricular fibrillation has been observed to follow the intravenous use of procaine amide,[153] and it is suggested that this agent, like quinidine, may cause ventricular fibrillation [154] or cardiac arrest.[155]

The toxic reactions to the local anesthetic agents range from moderate skin manifestations to more serious allergic responses, such as an anaphylactic reaction, which may terminate fatally.‖ Although effective against central stimulation, the barbiturates do not protect against the anaphylactic type of response. Close observation of the patient must be maintained in order that the type of untoward response can be properly diagnosed and the appropriate treatment instituted.

NARCOTICS AND ANALGESICS

The more commonly used opium alkaloid analgesics include morphine, dihydromorphinone (Dilaudid), metopon, and racemorphan (Dromaran), the last three representing chemically modified morphine structures. Racemorphan is reported to be a more powerful and longer-acting analgesic but a less potent hypnotic than morphine.¶ These agents are addicting. The so-called nonopiate addicting analgesics include meperidine (Demerol) and methadone (Dolophine). Both agents are effective analgesics,[161] although the latter is more potent. An acetyl derivative of the corresponding alcohol of methadone provides morphine-like action, which may persist for 24 to 72 hours.# The majority of these drugs are parasympathomimetic, the exception being meperidine, which relaxes the smooth muscle of the gastrointestinal tract. The incidence of nausea and vomiting is less frequent after meperidine administration than when morphine and certain of its derivatives are used. For this reason meperidine has been recommended as the analgesic of choice for intraocular surgery.[164]

Another morphine derivative, nalorphine (Nalline), acts as a potent antidote to all of the above drugs.* Successful treatment of acute heroin (diacetyl morphine) poisoning with this agent has also been reported.[170] Although depressing respiration in the normal subject,[171] nalorphine appears to block successfully the respiratory depression caused by an overdose of the addicting analgesics. This antidotal action is quite specific, since nalorphine is not particularly effective in combating the respiratory depression caused by other drugs, such as the barbiturates. Nalorphine inhibits the gastrointestinal motor activity induced by the addicting analgesics.† The urinary excretion of morphine by experimental animals is promoted by nalorphine.[174] The agent may prove useful in the early detection of addiction, since it appears to unmask a physical dependence on morphine and other addicting drugs and may in man precipitate an acute abstinence syndrome during addiction.‡ Used concurrently with one of the addicting analgesics, nalorphine blocks the unwanted

§ References 149 through 152.

‖ References 156 through 158.

¶ References 159 and 160.

References 162 and 163.

* References 165 through 169.

† References 172 and 173.

‡ References 175 and 176.

side-effects while not appreciably altering the degree of analgesia. Animal experiments have indicated that the development of a resistance to the analgesic effect of a mixture of morphine and nalorphine occurs more rapidly than when morphine is used alone.[177]

Trichloroethylene has been recommended as an analgesic in the practice of ophthalmology because it is convenient to use and rarely produces unpleasant after-effects.[178] Trichloroethylene is not new,[179] but its value as an analgesic in obstetric and office practice is being reported with increasing frequency.§ For analgesia the patient inhales through a special inhaler or a gauze saturated with the liquid and can very readily control his own dose. While trichloroethylene also has anesthetic properties, its use in concentrations sufficient to produce anesthesia has not been recommended,[183] since cardiac and respiratory difficulties may arise.‖

Of the antirheumatic analgesics, the salicylates are the most widely used. The pharmacology of the salicylates has been recently reviewed.[186] Particularly valuable in the treatment of rheumatic fever, they are effective against other rheumatic disorders as well.¶ Although evidence that the salicylates act upon the pituitary-adrenal axis continues to accumulate,[189] it is likely that these compounds exert some direct effect on the rheumatic disorders. In certain respects the salicylates and cortisone have quite opposite effects on cellular metabolism, particularly carbohydrate metabolism.[190]

Phenylbutazone (Butazolidin) can also be included among the antirheumatic analgesics, although, like the salicylates, its action in the rheumatic disorders is not due solely to its analgesic properties.[191] Phenylbutazone has a direct effect on the kidney tubule, promoting the excretion of uric acid, blocking the excretion of paraaminohippuric acid, and increasing sodium retention.# Phenylbutazone has little effect on carbohydrate metabolism.[197] Its therapeutic action does not appear to result from an increased secretion of corticosteroids.[198] The drug is very effective in the treatment of various rheumatic disorders, particularly acute gout.* Its use in the ocular manifestations of this disease would seem indicated when other treatment has failed. Benefit from the use of a combination of phenylbutazone and aminopyrine in the treatment of a variety of ocular diseases (for which cortisone would generally be prescribed) has been reported.† The incidence of toxic reactions to the drug, however, is high. The more serious complications include agranulocytosis ‡ and eruption of an acute peptic ulcer with possible perforation.§ Several fatalities have been recorded.‖ Retention of sodium may predispose to cardiac failure in those patients with limited cardiac reserve. Dermatologic and other manifestations of toxicity have also been noted.¶ In short, the toxicity of phenylbutazone is such that it should be used only in selected cases, under careful supervision.

§ References 180 through 182.
‖ References 184 and 185.
¶ References 187 and 188.
# References 192 through 196.
* References 199 through 202.
† References 203 and 204.
‡ References 205 through 209.
§ References 210 through 212.
‖ References 213 through 217.
¶ References 218 through 220.

SEDATIVES AND HYPNOTICS

The majority of reports on drugs of this group concern the barbiturates.

A thorough review of their metabolism and metabolic and physiologic effects has recently been published.# The barbiturates generally depress the respiration of nerve tissue to a degree which varies markedly with the particular drug. They also inhibit oxidative phosphorylation, a metabolic step which provides the cell with a store of readily available energy. This inhibition probably explains certain seemingly unrelated effects of the barbiturates at the cellular level.* The relationship of metabolic to clinical manifestations, however, is not certain. The sedative and anticonvulsant effect of the barbiturates appears to be due to a depression of the motor cortex, as well as to action lower in the central nervous system. The hypnotic effect, on the other hand, is probably mediated through the sleep centers of the diencephalon. The effects of the barbiturates on the autonomic nervous system include ganglion depression, anticholinergic action, and peripheral sympathetic blockade.† The sites of action of the barbiturates are thus many.

One of the major differences among the various barbiturates lies in the duration of their effect, which appears to be determined by both the tissue distribution of the compound and its rate of metabolism. Thus, pentobarbital (Nembutal) does not localize to so great a degree in body fat as does thiopental (Pentothal) and is not metabolized so rapidly by the human.[232]

For sedation prior to surgery, one of the medium-acting barbiturates is usually prescribed. Successful use of pentobarbital in children prior to ocular surgery is reported.[233] Continuous intravenous drip of pentobarbital during ocular surgery is said to provide controlled and satisfactory sedation on an average dose of somewhat less than 2 grains (0.13 gm.).[234]

The after-effects of barbiturate sedation and hypnosis vary with the drug, the dose, and the age of the patient. Mental impairment may follow a hypnotic dose for some hours,[235] and chronic barbiturate users may show a persistent impairment.[236] The more pronounced depression seen in barbiturate poisoning is most likely due to cerebral anoxia. Hence, it has been recommended that treatment of barbiturate intoxication should stress general supportive measures designed at overcoming the anoxia and cerebral edema, rather than the use of analeptics.[237] The latter drugs, however, do antagonize the physiologic effect of the hypnotic drugs and are recommended in certain instances, pentylenetetrazol (Metrazol) being the drug of choice.‡ Specific sensitivity to barbiturates may also produce serious reactions.[240]

Methylparafynol (3-methyl-pentyn-ol-3; Dormison) is a relatively new hypnotic agent which can be given in rather high doses with apparent safety,§ although fatal poisoning due to a suicidal overdose has been reported.[244] Anticonvulsant properties have been described,‖ but the drug is said to have little sedative action.

References 221 through 225.

* References 226 and 227.

† References 228 through 231.

‡ References 238 and 239.

§ References 241 through 243.

‖ References 245 and 246.

CHEMOTHERAPEUTIC AGENTS

ANTIBIOTICS AND SULFONAMIDES

Mode of Action.—A review of this subject has recently appeared.[247] Some antibiotics (polymyxins) have surface activity and exert their bactericidal effect by altering the permeability characteristics of the plasma membrane of the bacterial cell.¶ For the most part, however, the antibacterial nature of chemotherapeutic agents derives from their action as antimetabolites or enzyme inhibitors. The sulfonamides and certain antibiotics act as antimetabolites,[250] and their antibacterial activity can be overcome by the addition of a particular metabolite. For example, riboflavin and a number of other compounds have been shown to negate the inhibition by various antibiotics of the growth of Escherichia coli.[251] However, because of the chemical diversity of antibiotics and the variety of metabolic effects which they produce in various bacteria,# it is clear that competitive inhibition cannot account for the antibacterial activity of all of the antibiotics, or even of any one antibiotic against all bacteria. The alternative, i. e., enzyme inhibition, appears to account for the antibiotic activity in the majority of instances. The antibiotics do not alter phagocytosis.[257]

The growth stimulation which antibiotics, particularly the broad-spectrum antibiotics, induce in certain domestic or experimental animals and fowls appears to be due to some alteration of the intestinal flora.* Improvement in nitrogen absorption from the intestine may be a factor.[264]

Bacterial Resistance.—The increasing frequency with which strains of staphylococci resistant to various antibiotics are isolated continues to be reported.† A recent report has demonstrated a rising incidence of strains of staphylococci resistant to such antibiotics as penicillin, chlortetracycline, and oxytetracycline, but a declining incidence of resistance to chloramphenicol,[267] due, no doubt, to decreased use of the latter. This apparent increase in the incidence of resistance to the commonly used antibiotics gives no cause for alarm, however. It has been pointed out that the bulk of such data is obtained in hospitals, and that often the occurrence of cross infections among patients and hospital personnel has contributed to the high incidence of resistant organisms.[268] Moreover, the development of newer antibiotics has kept pace with the increase of resistance, and when the antibiotics are considered as a group, rather than individually, the incidence of resistance has actually decreased.[269] This serves further to emphasize the need for adequate laboratory studies in the management of infections.‡

The mechanism of resistance depends upon the organism, its environment, and the antibiotic, and varies from a bacterial mutation to the production of an antibiotic-destroying enzyme by the microbe.§ Specific attempts to induce a resistance to penicillin in strains of Treponema pallidum have failed,[278] this organism being the notable exception to the general pattern of increasing resistance to specific antibiotics.

¶ References 248 and 249.
# References 252 through 256.
* References 258 through 263.
† References 265 and 266.
‡ References 270 and 271.
§ References 272 through 277.

Absorption and Tissue Distribution.—With the exception of streptomycin and the polypeptides, such as the polymyxins and bacitracin, oral administration provides adequate serum levels of most antibiotics.|| Of the various orally administered penicillin preparations, penicillin G produces the highest blood levels, although oral administration of other derivatives has been demonstrated to be effective clinically.¶ The tissue distribution of the antibiotics is generally that which would be predicted for compounds which pass cellular barriers poorly. For example, carbomycin readily penetrates into ascitic fluid but does not enter the cerebrospinal fluid.[286] The β-diethylaminoethyl ester of penicillin G (penethamate) is one exception. It readily enters the erythrocyte and reaches relatively high concentrations in lung tissue.# It cannot be stated, however, that this high concentration in the lung provides any added benefit in the treatment of pneumonia.

Penethamate readily enters the spinal fluid,[289] and presumably penetrates with equal facility into the eye. In the light of present knowledge, the antibiotic which most readily crosses the blood-aqueous barriers is chloramphenicol. It also gives the highest intraocular concentration after subconjunctival injection.* Among the sulfonamides, the pyrimidine derivatives (sulfadiazine, sulfamerazine, sulfamethazine) enter the eye in highest concentration.

Hazards of Antibiotic Therapy.—Two distinct hazards must be considered. The first is the possible development of a superimposed infection with resistant bacteria (particularly strains of staphylococci and Pseudomonas aeruginosa) or with certain fungi and yeasts, particularly Candida albicans.† Fatal results may ensue during systemic therapy with antibiotics from any of these infections. They appear to be caused by a disturbance of the normal flora which permits the overgrowth of resistant, and originally less virulent, organisms.[296] The reported high incidence of Gram-negative bacilli in intraocular infections following surgery may represent a similar sequence.[297] Oxytetracycline and chlortetracycline enhance the virulence of C. albicans, particularly if cortisone is concurrently administered.‡

The other major hazard of antibiotic therapy concerns the untoward reactions to the antibiotics themselves. Such reactions to penicillin therapy are by far the most frequently reported. Indeed, penicillin is said to be the commonest cause of drug allergy.[301] Reactions to it vary from mild cutaneous manifestations to anaphylactic shock and death.§ These are oftenest seen in patients with a history of allergic tendencies. The adverse reactions to penicillin are said to be less frequent when the drug is used orally.[312] Sensitivity tests, such as patch or scratch tests, are helpful but serious sequelae may develop even in the absence of a positive skin test.|| The possibility has been raised that certain diseases, such as periarteritis,

|| References 279 and 280.

¶ References 281 through 285.

References 287 and 288.

* References 290 and 291.

† References 292 through 295.

‡ References 298 through 300.

§ References 302 through 311.

|| References 313 through 315.

presumably due to a tissue hypersensitivity, may result from penicillin.[319] Penicillin therapy in penicillin-sensitive patients is often made feasible by the use of an antihistaminic or one of the hypoallergenic penicillins.¶

Streptomycin may cause cutaneous allergy and occasionally an aplastic anemia,[322] but its most significant toxic manifestation is on the eighth cranial nerve. The vestibular portion of this nerve is most affected by streptomycin, while dihydrostreptomycin is most toxic to the auditory portion.# Clinically, the two differ very little, although streptomycin is perhaps less toxic.* Reported adverse responses to chloramphenicol include bilateral optic neuritis,[327] but a more serious manifestation (depression of the bone marrow activity) limits the systemic use of this drug to treatment of those infectious diseases which are refractory to other forms of treatment but sensitive to chloramphenicol.† Aside from gastrointestinal disturbances, the toxic manifestations of the tetracyclines are rare.‡ Cutaneous sensitization has been no great clinical problem. In persons with normal renal function no ill-effects follow the parenteral administration of polymyxins B and E in doses up to 2.5 mg. per kilogram.§ However, these drugs are nephrotoxic, and in the presence of renal damage smaller doses are recommended. Cutaneous sensitivity to sulfonamides has been reported often in previous years; more bizarre manifestations of sulfonamide sensitivity include polyneuritis and arteritis.[338]

Clinical Use.—It is generally recommended that the topical use of antibiotics about the eye be limited to those whose systemic use is relatively infrequent and which rarely induce a cutaneous hypersensitivity. A list of such drugs includes bacitracin, neomycin, the polymyxins, and chloramphenicol. To it should be added chlortetracycline and oxytetracycline,|| since they rarely induce local sensitivity. Certain sulfonamides have given good results also.¶

The newer antibiotics erythromycin and carbomycin have shown their greatest merit in the treatment of staphylococcal infections resistant to penicillin and other antibiotics.# Indeed, this clinical situation probably constitutes the primary indication for their use. Infections with other cocci may respond to these antibiotics, although often not so effectively as to penicillin.* Of the two, erythromycin appears to give the better results.† It is effective when used locally.[355] The new broad-spectrum antibiotic tetracycline has a bacterial spectrum similar to oxytetracycline and chlortetracycline.[356] Cross resistance among the three may be encountered.[357] Tetracycline causes fewer gastrointestinal disturbances than the other generically related compounds.‡

Other than those due to antibiotic-resistant staphylococci, the majority of clinically troublesome infections are caused by Gram-negative organisms. Their preva-

¶ References 317 through 321.
# References 323 and 324.
* References 325 and 326.
† References 328 through 331.
‡ References 332 and 333.
§ References 334 through 337.
|| References 339 and 340.
¶ References 341 and 342.
# References 343 through 346.
* References 347 through 352.
† References 353 and 354.
‡ References 280 and 358.

lence in postsurgical intraocular infections has been mentioned.[297] Of these, Ps. aeruginosa may prove the most resistant to treatment. External ocular diseases due to this organism, particularly corneal ulcerations, have generally responded to the polymyxins.§ Either topical or subconjunctival administration of the drug may be effective in such cases. However, intraocular penetration of the drugs by any route is undoubtedly poor, and intravitreal injection of polymyxins may be the only choice in panophthalmitis due to this organism. The use of neomycin, the tetracyclines, chloramphenicol, streptomycin, or sulfonamides may be beneficial in the treatment of infection due to Gram-negative bacilli.‖

Penicillin remains the most effective treatment of both early and late syphilis.¶ The broad-spectrum antibiotics are also useful but should be reserved for those patients who are sensitive to penicillin.# Penicillin therapy of syphilitic optic atrophy is reported to be successful provided that the initial vision is better than 6/20.[375]

Infections caused by the smaller viruses generally do not respond to antibiotic agents, although successful chlortetracycline treatment of vaccinia of the eyelid has been reported.[376] Certain synthetic polypeptides have been shown to be effective against the mumps virus in experimental situations,[377] but nothing for clinical use has appeared. The broad-spectrum antibiotics may affect the larger viruses, however.* These include the virus of trachoma, whose treatment by such drugs continues to be reported.[380] However, a comparative study has suggested that the sulfonamides may be somewhat superior to the antibiotics.[381]

Successful treatment of actinomycosis with penicillin, sulfonamides, chlortetracycline, and oxytetracycline has been reported.†

Combinations of Antibiotics.—This subject has been reviewed.[385] As an approach to the problem of combined use of antibiotics, two groups of these drugs can be distinguished. Group 1 includes penicillin, streptomycin, bacitracin, and neomycin. Members of this group are often synergistic, never antagonistic. Group 2 includes chlortetracycline, chloramphenicol, and oxytetracycline. These are neither synergistic nor antagonistic to one another. Erythromycin and carbomycin have been shown to fall in the second group,[386] while polymyxin does not fit well into either group. Obviously, combinations within Group 1 may be helpful and within either group will do no harm. Such combinations are available. A mixture of neomycin and bacitracin has been successfully used in ocular disease.[387] Benefit in dermatologic disease from topical application of a mixture of oxytetracycline and polymyxin B has also been reported.[388] On the other hand, the combining of a member of Group 1 with a member of Group 2 may produce less clinical response than the use of either drug alone. In the final analysis, then, laboratory guidance is indispensable.‡

§ References 359 through 362.

‖ References 363 through 366.

¶ References 367 through 371.

References 372 through 374.

* References 378 and 379.

† References 382 through 384.

‡ References 389 through 391.

Isonicotinic Acid Hydrazide (Isoniazid)

A number of reports have attested to the clinical benefit of a combination of isoniazid with streptomycin in the treatment of pulmonary tuberculosis.§ When they are so employed, the development of bacterial resistance to either drug appears to be retarded.‖ Isoniazid is bacteriostatic rather than bactericidal, its effect apparently being due to interference with the function of an essential metabolite.[404] Experimental studies have indicated that the strains of Mycobacterium tuberculosis resistant to isonicotinic acid hydrazide are less virulent than more sensitive strains.¶ Isoniazid does not alter the sensitivity to tuberculin.[409]

Isoniazid readily passes cellular barriers, effective concentrations being produced in various secretions and in the cerebrospinal fluid.# Administered with streptomycin, it is the treatment of choice for miliary tuberculosis and tuberculous meningitis. Reported results indicate a definite superiority of such drug combinations over streptomycin alone, particularly in the treatment of tuberculous meningitis.*

Isoniazid penetrates reasonably well from the blood stream into the eye, a relatively high concentration in the aqueous humor being attained.[418] Its benefit in the treatment of experimental ocular tuberculosis has been demonstrated.[419] Successful isoniazid treatment of uveitis of presumedly tuberculous etiology has been reported.[418] It is recommended that suspected tuberculous uveitis be treated with a combination of isoniazid and streptomycin.

Isoniazid is said to be beneficial in the treatment of both experimental and clinical leprosy.† It probably is of little value in the treatment of sarcoidosis (Edelson [422]; Israel and others [423]). Therapeutic benefit in actinomycosis [424] and in chronic discoid lupus erythematosus [425] is claimed for isoniazid.

The standard dose (5 mg. per kilogram) of isoniazid can be administered for many months without apparent damage to the liver, kidneys, bone marrow, or central nervous system.[426] However, peripheral neuropathy has been reported.‡

HORMONES

Corticotropin, Cortisone, Hydrocortisone

General Nature of the Hormones.—Corticotropin is elaborated by the pituitary gland under the control of the hypothalamus and the level of the circulating corticosteroids.§ It is protein in nature, although several peptides of varying molecular weight have exhibited similar biologic activity. Normally, corticotropin rapidly disappears from the blood stream, the biologic half-life of endogenous corticotropin being somewhat less than one minute,[432] but its ultimate fate is unknown. Corticotropin has been observed to accumulate in experimentally inflamed areas,[433] manifesting a direct local action, e. g., a decrease in diapedesis of leucocytes. The clinical significance of such local action is obscure, however, and its primary effect appears to be on the adrenal cortex.

§ References 392 through 401.
‖ References 402 and 403.
¶ References 405 through 408.
# References 410 and 411.
* References 412 through 417.
† References 420 and 421.
‡ References 427 through 429.
§ References 430 and 431.

Under the influence of corticotropin, the adrenal cortex is stimulated to produce a variety of steroids, 17-hydroxycorticosterone (hydrocortisone) being released in the largest quantity. Analysis of the plasma from adrenal vessels has indicated that the normal human adrenal gland elaborates between 15 and 25 mg. of 17-hydroxycorticosteroids daily.[434] This is sufficient to give a plasma concentration of 3 to 26 γ per 100 ml.[435] Since ascitic fluid contains only 3 to 5 γ per 100 ml., one can conclude that the hormones do not distribute themselves freely in extracellular water.[436] Still lower concentrations of cortisone and hydrocortisone have been detected in the cerebrospinal fluid.[437]

Corticotropin also causes a depletion in the ascorbic acid content of the adrenal gland of experimental animals, measurement of which provides an assay of corticotropin activity. This drop in the adrenal ascorbic acid content has been observed to occur in the human as well.[438] The relationship of the ascorbic acid depletion of the adrenal cortex to the production of steroids is obscure. The adrenal glands of scorbutic guinea pigs contain virtually no ascorbic acid; yet the 17-hydroxycorticosteroid concentration in the plasma of these vitamin-deficient animals is higher than that of normal guinea pigs.[439] Even in fully scorbutic guinea pigs, exogenous corticotropin stimulates the excretion of 17-ketosteroids.[440] Variations in the therapeutic potency of corticotropin preparations standardized by the animal assay have been reported.[441] This discrepancy might be expected if the two activities (therapeutic effect and adrenal ascorbic acid depletion) are not due to the same biologic stimulus.

Metabolic and Tissue Effects.—The 17-hydroxycorticosteroids have a marked catabolic, and possibly an antianabolic, effect on most phases of metabolism at the cellular level. The effect on protein metabolism is evidenced by an increase in the free amino acids of serum and many tissues.[442] Whether this catabolic action is overcome by vitamin B_{12} is debatable.‖ Evidences of gluconeogenesis present to a degree which depends on the diabetic tendency of the individual subject.[445] Alterations in electrolyte metabolism include increased excretion of potassium and retention of sodium.¶ Cellular potassium is depleted, the ion being to some extent replaced by sodium. This exchange across the cellular barrier is not mediated solely by the kidney, for direct cellular effects of these hormones on cation exchange can be demonstrated both in vivo and in vitro.# A calcium and phosphorus deficit may also result from administration of the 17-hydroxycorticosteroids.[452]

Among the tissue effects of the 17-hydroxycorticosteroids and corticotropin is a depression of the uptake of I^{131} and a decreased clearance of radioiodine by the thyroid.* This depression is apparently not due to any inhibition of thyrotropin and causes no change in the thyroid status. The hormones have a marked effect on the formed elements of the blood, particular attention being paid to the eosinopenia which they cause.† Although the degree of this eosinopenia is often used as a measure of cortisone or corticotropin effect, parallels between the anti-inflammatory, the metabolic, and the eosinopenic responses are not always demonstrable. In addition, cortisone, hydrocortisone, and corticotropin may induce a leucocytosis.

‖ References 443 and 444.
¶ References 446 through 450.
# References 451 and 452.
* References 454 and 455.
† References 456 through 459.

However, they do not prevent, but rather enhance, the leucopenia which nitrogen mustard may cause.[460] It is interesting to note that cortisone prevents the destruction of red blood cells caused by the administration of phenylhydrazine to adrenalectomized rats.[461] It also has a stimulatory effect on the production of thrombocytes. This is most marked in persons with idiopathic thrombocytopenic purpura, and cortisone is therapeutically useful in these patients, particularly prior to surgery.‡ Among other reported tissue effects during cortisone administration is an increased susceptibility of the liver to damage by carbon tetrachloride.[465]

Anti-Inflammatory Effects.—Since the anti-inflammatory effects of the 17-hydroxycorticosteroids do not always parallel their metabolic effects, it is reasonable to suppose that a compound can be produced which will retain the anti-inflammatory activity of the 17-hydroxycorticosteroids but be devoid of metabolic influence. Such a compound has not been found, although certain substances have been shown to modify the metabolic activity of cortisone.§ Administered cortisone is found to accumulate in artificially inflamed areas of experimental animals. Here it alters the inflammatory response, presumably by inhibiting the activity of leucotaxin, and thus preventing the increase in capillary permeability and cellular migration which this substance normally produces.[468] In addition, cortisone appears to maintain vascular tone. The reduction of oxygen consumption induced by cortisone in granulation tissue probably reflects changes in the type and number of individual cells rather than any specific metabolic effect.[469] Experimental studies have indicated that the growth of fibroblasts in tissue culture is not inhibited by cortisone or 17-hydroxycorticosterone, although they appear to diminish the migration of these cells in vitro.[470] In the final analysis, then, the formation of granulation tissue is reduced more in degree than in kind.[471] By this suppression of the inflammatory response, cortisone reduces many of the serious sequelae of inflammation.‖ At the same time, a readier dissemination of both bacterial and viral infections occurs.¶ This is due in part to a reduction in the physical barrier which inflammation provides. Phagocytosis is probably not decreased by hormone administration,# although the phagocytosed bacteria are apparently made more resistant to destruction.[482] The hormones do not alter the production of antibodies to bacteria,* nor do they significantly affect the physiologic response to diphtherial and tetanus exotoxins † or to endotoxins.[488]

The corticosteroids probably afford protection from both the inflammatory and the allergic responses in a similar way, although uncertainty concerning the etiology of many allergic conditions hampers a full understanding in this respect. Certain conclusions are permissible, however. First, these agents do not generally alter the production of antibodies to sensitizing antigens (although certain exceptions occur ‡), nor do they inhibit the antigen-antibody reaction.[491] More likely, the drugs modify the sequelae of this reaction. Second, cortisone and hydrocortisone do not appre-

‡ References 462 through 464.
§ References 466 and 467.
‖ References 472 and 473.
¶ References 474 through 477.
# References 478 through 481.
* References 483 and 484.
† References 485 through 487.
‡ References 489 and 490.

ciably alter the tissue effect of histamine or the type of allergenic response presumably due to histamine release. Third, their most marked effect is against allergic phenomena, such as the tuberculin reaction and certain drug sensitivities,§ in which a histamine release presumably plays no part. Nonetheless, several clinical conditions, e. g., pollen sensitivities, whose most likely etiology is a histamine type of response, are reported to respond to cortisone.‖ However, the role of the corticosteroids in the therapy of these conditions is not firmly established. The use of a mixture of corticosteroids and antihistaminics in the treatment of a variety of allergic conditions, including ocular manifestations, has been reported.¶ In general, antihistaminics have been of little value in the treatment of allergic diseases of the eye, and the benefit of combined therapy must await further evaluation.

Clinical Use.—A general review covering the clinical use of these drugs has appeared.[501] The most predictable and pronounced responses to corticotropin are achieved by the intravenous drip and the use of repository or long-acting corticotropin products.# The marked physiologic effect of the latter is due to continuous stimulation of the adrenal glands.

Both hydrocortisone and cortisone are now available in quantity for oral, parenteral, or local use. When hydrocortisone is administered orally, the maximum blood level is reached in 45 to 60 minutes and returns to normal in 4 to 6 hours.[505] In general, hydrocortisone has a more potent metabolic and anti-inflammatory effect than cortisone. However, experimental studies comparing local effects of cortisone and hydrocortisone on the eye have failed to demonstrate a significant difference between the two,[506] although instances have been reported in which hydrocortisone was clinically beneficial after cortisone therapy had failed.* It is interesting that the clinical response to the two is so similar in ocular disease, whereas when the drugs are applied locally to other tissues the superiority of hydrocortisone over cortisone is pronounced.† (This superiority of hydrocortisone in other than ocular tissues is not due to any difference in local absorption of the compounds.[510]) The comparative effects on the eye of the free alcohols of the 17-hydroxycorticosteroids and their acetates has not been studied specifically. A comparison of their dermatologic effects has indicated that the acetate is more potent.[511]

Cortisone, hydrocortisone, and corticotropin provide most dramatic results in the treatment of an inflammatory or a hypersensitivity response. While there is no question that the blocking of inflammation is generally desirable, particularly in ocular disease, the question of whether it is always desirable has not necessarily been answered. For example, by a special technique hydrocortisone has been shown to enhance necrosis of the skin resulting from the injection of chemical irritants into experimental animals,[512] presumably by preventing the barrier to necrosis which inflammation may establish. Another danger of blocking of the inflammatory process is the increased dissemination of an infectious process. Where an infectious process can be controlled chemotherapeutically, the use of cortisone to control the sensitivity

§ References 492 through 494.

‖ References 495 through 497.

¶ References 498 through 500.

References 502 through 504.

* References 506 and 507.

† References 508 and 509.

response to the organism is considered justified.‡ However, further clinical experience is needed because there are indications that cortisone, by blocking the body's response to pathogenic organisms, reduces the effectiveness of chemotherapeutic drugs.§

With these reservations, then, the major indication for these hormones in the treatment of ocular disease is the prevention of the serious complications and sequelae of an inflammatory process, particularly one induced by hypersensitivity.‖ Among the disease processes reported to be successfully treated with these drugs are iridocyclitis,[519] acute neuroretinitis,[520] and ocular paralysis [521] associated with sarcoidosis, paralysis of ocular muscles apparently of inflammatory etiology,[522] Reiter's syndrome,[523] Sjögren's syndrome,[524] Bell's palsy,¶ angioneurotic edema of the orbit,[527] temporal arteritis,[528] and neuromyelitis optica.[529] Cortisone has been reported to have both therapeutic and diagnostic value in cases of so-called thyrotropic exophthalmos,[530] but this has not been universally observed.# Indeed, cortisone production of exophthalmos in experimental animals has been described.* Occasional reports of therapeutic benefit in the treatment of degenerative lesions appear.[535] It is worthy of mention that adverse ocular side-effects from use of these agents are only rarely reported.[536]

Generally, the absolute and relative indications for the use of these hormones have become more sharply defined, and as a consequence the frequency of their use has declined in many fields.† The possibility of serious sequelae from their metabolic effects, as well as the not infrequent observation that a severe rebound may follow cessation of therapy, has dictated that their use be reserved for more serious conditions which do not respond readily to other forms of therapy. Moreover, reevaluation of the comparative merits of hormonal as against other forms of therapy, e. g., salicylates in rheumatic fever, has in certain instances failed to demonstrate a great difference in clinical response.[539] Still, these hormones have well-documented value in the treatment of certain rheumatic disorders, collagen diseases, allergic disturbances, and endocrine dysfunctions. In addition, the agents are reported to be of benefit in such conditions as thyroiditis, either acute or subacute,‡ keloids,[544] tabetic crises,§ herpes zoster,[547] Rh incompatibilities during pregnancy,[548] snake venom poisoning,[549] and such drug reactions as serum sickness [550] and agranulocytosis.[551]

Complications of Therapy.—The major complications which may occur during the administration of these compounds arise from their metabolic effect. These include sodium retention, potassium depletion, and, less frequently, a calcium deficiency.‖ In general, the metabolic effects of these agents can be overcome by judicious dietary measures, such as high protein, high potassium, and low salt intake.¶ It has been recognized that an acute adrenal insufficiency may be precipitated by

‡ References 513 and 514.
§ References 515 and 516.
‖ References 517 and 518.
¶ References 525 and 526.
# References 531 and 532.
* References 533 and 534.
† References 537 and 538.
‡ References 540 through 543.
§ References 545 and 546.
‖ References 552 and 553.
¶ References 554 and 555.

a stress, such as surgery, in a patient on cortisone therapy.# The preoperative administration of extra cortisone to such a patient should be routine. The danger of the spread of a septic process,* particularly from a tuberculous focus, must always be kept in mind. The development, reactivation, or perforation of a peptic ulcer continues to be reported.† Mental disorders may be troublesome.[562] A case of aplastic anemia supposedly due to the administration of corticotropin has demonstrated that it may act as an allergen.[563] Pregnancy appears to offer no contraindication to the administration of cortisone and corticotropin.[564]

Other Steroid Hormones

The other steroid hormones of interest include testosterone and progesterone. The male sex hormone, testosterone, is an androgenic substance and promotes nitrogen retention. In this respect, therefore, it has the opposite effect of cortisone. The hormone has been tried in the treatment of diabetic retinopathy, and, although certain benefit was early reported, more recent studies have not substantiated the previous work.[565] Possible benefit in the treatment of interstitial keratitis with testosterone has also been suggested.[566]

Recent studies have implicated progesterone in the control of intraocular pressure. Thus, it has been found that the facility of outflow of aqueous appears to be increased in the progestational period of the menstrual cycle.[567] In the same study, the administration of progesterone was shown to lower the intraocular pressure in certain instances.

Thyroid and Antithyroid Drugs

Thyroxin is released from the thyroid gland under the stimulus of the thyroid-stimulating hormone elaborated by the pituitary.[568] The exact manner by which thyroxin causes a calorigenic catalysis is not known.[569] No effect of thyroid added in vitro can be detected, although the injection of thyroxin leads to an increased respiratory rate in some (but not all) tissues.[570] When thyroid is given to a euthyroid subject in doses of approximately 2 grains (0.13 gm.), little clinical response is observed, since the thyroid gland is inhibited. The exact cause of this inhibition is still in dispute, but the weight of evidence favors the view that the elaboration of thyroid-stimulating hormone is depressed.[571] The latter concept constitutes the basis for the use of thyroid in instances of exophthalmos of the so-called thyrotropic type. However, the weight of current evidence, experimental and clinical, favors the view that the exophthalmos-producing factor of the pituitary is not thyrotropin.‡ It is for this reason that the treatment of a malignant exophthalmos by thyroid is not routinely successful.§ Probably the use of this compound should be limited to those patients who show evidence of thyroid deficiency. (In the evaluation of the thyroid status of the patient by other than clinical means, the most dependable laboratory tests are the estimation of the protein-bound serum iodine and the uptake of radioactive iodine by the thyroid gland.[575] The basal metabolic rate is less exacting.)

The antithyroid drugs include radioactive iodine, the action of which has been covered in another section. The pharmacologic effect of this agent depends upon its

References 556 and 557.
* References 558 and 559
† References 560 and 561.
‡ References 572 and 573.
§ References 572 through 574.

incorporation into, and destruction of, the secretory cells of the thyroid gland.[576] The major advantage of its use lies in the graded and controlled thyroidectomy which can be accomplished with radioiodine. The major disadvantage is a possible carcinogenesis.[577] In addition to I^{131}, there are a variety of antithyroid drugs known. These include thiouracil and derivatives, such as methylthiouracil or propylthiouracil, methimazole, neomercazole, thiocyanate, and resorcinol. Clinically, the first three have been most widely used.‖ The disadvantages of their use include a tendency to relapse following cessation of therapy.[583] The effect of these drugs on the exophthalmos associated with thyroid disorders is not certain. Neither radioiodine nor the other antithyroid drugs prevent exophthalmos.[584] As is true after surgery, exophthalmos may progress or regress during treatment with these agents, but no rule as to their use in its management can be established. Perhaps the thyroid status of the patient is of little significance. The fundamental difficulty lies in a lack of understanding of the etiology of the exophthalmos associated with thyroid disorders ¶ and the absence of diagnostic tests which will permit a better evaluation of the prognosis.

AUTONOMIC DRUGS

Cholinergic and Parasympathomimetic Drugs

The pharmacology of these drugs with special reference to their ocular action [587] and their use in the treatment of chronic glaucoma [588] has been reviewed. Generally, two groups can be considered: the cholinergic group, which acts directly on the effector cell, and the parasympathomimetic group, the anticholinesterases, which permit the accumulation of acetylcholine. Pilocarpine, carbachol, and methacholine exemplify the first group and diisopropyl fluorophosphate, physostigmine, and neostigmine, the latter.

Both in the cat [589] and in man [590] an additive effect of small doses of pilocarpine and physostigmine on the iris sphincter has been demonstrated. On the other hand, when the iris musculature of the rabbit is stimulated maximally with pilocarpine, an additional response to the anticholinesterases is not seen, even though the latter drugs when administered alone may produce a greater degree of miosis than does pilocarpine.[591] The results support the view that the points of action of pilocarpine and of acetylcholine on the smooth muscle fiber are different, that in weak concentrations the effects of the two may summate, but that when responding maximally to one agent (pilocarpine), the muscle fiber is refractory to the action of an even more potent drug. In this sense the drugs are competitive. It should be emphasized that the effects described refer simply to the miotic, and not necessarily to the ocular hypotensive, action of these drugs. Indeed, the mechanism by which these drugs reduce the ocular tension in many instances is not known. Pilocarpine and physostigmine lower the episcleral venous pressure,[592] and this must account, at least in part, for their ocular hypotensive effects.

Acetylcholine is seldom used by itself because of its evanescent action. Instances of extraocular and intraocular muscle paralysis and corneal anesthesia following retrobulbar injection of acetylcholine for occlusion of the central retinal artery are reported.[593]

‖ References 578 through 582.

¶ References 585 and 586.

A review of the cholinesterases and the mode of action of anticholinesterases has appeared.[594] The cholinesterase content of the iris is appreciable and is reduced after postganglionic parasympathetic denervation. This same result occurs when the superior cervical ganglion is removed, the pseudocholinesterase content being primarily affected.[595] The suggestion is made that the hypersensitivity of the sympathectomized iris to epinephrine may be due to this fact, although a decrease in amine oxidase, the enzyme which destroys epinephrine, is certainly a contributing factor.

Certain complications from the ocular use of the anticholinesterases have been reported. These include an acute rise in tension following the instillation of diisopropyl fluorophosphate into an eye with narrow-angle glaucoma.[596] Although this effect is presumably vascular, the mechanism is uncertain. These drugs may have some direct action on the vascular tree. An interesting study has indicated that antidromic vasodilatation (in the rabbit's ear) is reduced by the cholinesterase inhibitors, such as physostigmine, neostigmine, and diisopropyl fluorophosphate,[597] an effect not considered due to the accumulation of acetylcholine. The appearance of unusual behavior patterns in children and the development of iris cysts, even from small doses of diisopropyl fluorophosphate, have been reported.[598] The organic phosphates, such as diisopropyl fluorophosphate, inhibit cholinesterase activity of central nervous tissue.[599] Whether an unusual behavior pattern may be due to this action cannot be stated.

The use of these drugs in the treatment of myasthenia gravis deserves comment. The localized ocular form of this disease may persist for a number of years with no general extension.[600] Although thymectomy may have some merit in myasthenia gravis,# medical management with anticholinesterases remains the most widely used treatment. Those agents most frequently used for this purpose are neostigmine, tetraethylpyrophosphate and octamethylpyrophosphoramide.[603] Edrophonium chloride (Tensilon), a substance which has much of the nicotinic but little of the muscarinic action of neostigmine, has been recommended as a test agent in the diagnosis and medical management of myasthenia gravis.[604]

Parasympathetic-Blocking Agents

Noteworthy studies of this group of drugs have concerned a new series of parasympathetic-blocking agents * of which cyclopentolate (Cyclogyl) is the prototype. In a 1% solution it produces a very effective cycloplegia of relatively short duration. The action of this series of drugs is probably due to a competitive inhibition of acetylcholine. They produce virtually no systemic side-effects, indicating that they may be inactivated locally. In general, a preferential action of the parasympathetic-blocking agents at some specific nerve ending cannot be demonstrated.[608]

Adrenergic and Sympathomimetic Drugs

The stimulating substance released at the sympathetic nerve endings is probably l-arterenol, although a species variation may occur. It can be identified in the ciliary body and the iris (of cattle eyes), but no evidence of either epinephrine or arterenol in aqueous humor (of cattle) can be detected.[609] On the other hand, epinephrine is the hormone released in greater quantity by the adrenal medulla.[610] The elaboration

References 601 and 602.

* References 605 to 607.

of these substances by this gland is markedly increased during asphyxia and after the administration of drugs which stimulate the autonomic ganglia.[611] Secretion is depressed when the blood glucose level is raised.[612]

Epinephrine induces an eosinopenia and a leucocytosis in man much as do corticotropin and the 17-hydroxycorticosteroids. This effect does not appear to be due to a stimulation of steroid release.† The eosinopenia following arterenol is less than that following epinephrine.[615]

When a structure is stripped of its sympathetic innervation, it becomes hypersensitive to epinephrine and arterenol. This appears to be due to a decrease in the tissue concentration of amine oxidase,[616] an enzyme which inactivates these drugs. The synergistic action of cocaine and epinephrine on the iris dilator fibers is considered to be due to the inhibition by cocaine of amine oxidase. This is supported by studies which have shown that cocaine enhances the effect of epinephrine and arterenol on the intestine but has only a variable effect on the response to other drugs, such as phenylephrine (Neo-Synephrine),[617] which normally are little altered by amine oxidase. On the other hand, cocaine is without effect on the blood pressure response to epinephrine.[618] Moreover, cocaine decreases the miotic action of methacholine on the sympathectomized iris.[589] In the final analysis the sympathomimetic action of cocaine is still uncertain.

Among the uses of the adrenergic agents in ophthalmology, mention has been made of their mydriatic effect.[619] Epinephrine (particularly with cocaine) applied locally in certain cases of glaucoma often causes a marked drop in the ocular tension. The mechanism here is not understood. Stimulation of the cervical sympathetic usually causes a sharp drop in intraocular pressure. Small intravenous doses of arterenol cause a slight rise in intraocular pressure coincident with the rise in blood pressure.[620] Epinephrine in similar dosage induces a biphasic blood pressure response and generally causes a drop in intraocular pressure. The changes in intraocular pressure induced in this manner, however, are generally transient, whereas the local effect may be prolonged.

Because of its pressor effect, arterenol is the drug of choice in the emergency treatment of vascular hypotension.‡ So potent is the vasoconstrictor action of the drug that ulceration of the skin may occur.[624]

Sympathetic-Blocking Agents

Among the peripheral sympathetic-blocking agents are the ethylamine chlorides, one of which, Dibenamine, is valuable in the treatment of certain cases of acute glaucoma. By a variety of techniques it has been shown that Dibenamine reduces aqueous formation.[625] The exact mechanism by which this effect is mediated is not known, however. Another peripheral blocking agent, totazoline (Priscoline), when given by retrobulbar injection relieves the pain of hemorrhagic glaucoma without lowering the ocular tension.[626] Its action in this regard is uncertain.

Ganglion-Blocking Agents

Tetraethylammonium chloride and hexamethonium are examples of that group of drugs which block transmission across the ganglia of both the sympathetic and the parasympathetic systems. (Atropine has ganglioplegic action that is weak as

† References 613 and 614.

‡ References 621 through 623.

compared with its anticholinergic effect.[627]) The two drugs are mostly employed for the sympathetic blockade they induce, however, hexamethonium being the most widely used. This drug reduces the ocular tension, the decrease probably being secondary to the vascular hypotension.

Hexamethonium is most widely employed in the treatment of hypertension. Many of the manifestations of the disease, such as hypertensive retinopathy, respond to the drug.[628] It is effective orally,§ but the parenteral route may be preferable. In addition, hexamethonium has been used to produce a bloodless surgical field.‖ Other, shorter-acting ganglioplegic compounds also are useful for this purpose.¶

For the medical treatment of hypertension, there are now available several agents which act at different levels of the nervous system.# The extracts of Rauwolfia serpentina appear to act at the cortical level; hydralazine and the alkaloids of Veratrum viride, on the hypothalamus; hexamethonium, at the autonomic ganglia, and the β-halo-ethylamines and others, at the postganglionic peripheral endings. Often various combinations of these have proved helpful.* The drugs are not without danger,† their toxic action ranging from excessive ganglion blockade (due to hexamethonium) to sensitivity reaction.

MUSCLE RELAXANTS

The neuromuscular-blocking agents and the ganglioplegic drugs have certain chemical similarities, and each has a dual action. Thus, the ganglion-blocking agents also have a weak action at the motor end-plate. Conversely, curare and the curare-like drugs block ganglion transmission to a small degree, but their peripheral effects are more pronounced.

The general pharmacology of the neuromuscular-blocking agents has been reviewed.‡ Generally they are divided into two groups. In one group are those which, like curare, are competitive with acetylcholine and for which neostigmine acts as an antidote. In the other group are the depolarizing agents, such as decamethonium and succinylcholine, against which neostigmine is not antidotal in man. Some agents appear to have both actions.[650] Of the competitive agents, the curare alkaloids are widely employed. They provide a relatively prolonged relaxation. Of the depolarizing group, the most commonly used is succinylcholine.§ This has a relatively short action, most likely because it is hydrolyzed by pseudocholinesterase. Because of its short action, the need for an antidote is reduced. However, an occasional patient may have a prolonged response to the drug.[655]

Many reports have appeared commending the use of the neuromuscular-blocking agents in ocular surgery.‖ It will be recalled that, of the striated muscles, the extraocular muscles are most sensitive to curare. The spread in dosage necessary to produce a therapeutic effect and respiratory depression is thus ostensibly widest

§ References 629 and 630.
‖ References 631 and 632.
¶ References 633 through 635.
# References 636 and 637.
* References 638 through 642.
† References 643 through 645.
‡ References 646 through 649.
§ References 651 through 654.
‖ References 656 through 658.

in ocular surgery. The curare alkaloids have no direct effect on the iris musculature, although in higher dosage ranges an action representative of autonomic ganglion blockade or asphyxia may be seen.[659]

MISCELLANEOUS DRUGS

Acetazoleamide (Diamox) is a potent carbonic anhydrase inhibitor and by virtue of this action reduces gastric and pancreatic secretion and promotes the renal excretion of sodium. For the latter effect it has been used clinically as an oral diuretic in congestive heart failure.¶ Bicarbonate is actively transferred into the aqueous humor (at least of the rabbit), carbonic anhydrase presumably catalyzing the transport, and an effect of acetazoleamide on aqueous formation might be anticipated. Injected intravenously into the rabbit, acetazoleamide causes a drop in the bicarbonate concentration of the aqueous humor.# However, the arterial plasma values may fall in approximately the same amount, and an action of the drug on aqueous formation cannot be inferred from these studies. Nonetheless, administered orally, the drug causes a profound drop in the intraocular pressure of many patients with glaucoma.[662] In addition to its use in acute cases, the drug may be employed as adjunctive therapy in those cases in which ocular tension is poorly controlled with miotics. In these instances a combination of the usual local measures and oral use of acetazoleamide has proved valuable.* Toxicity appears low. Paresthesias and drowsiness may be produced. A febrile reaction similar to that occasionally associated with sulfonamide administration has been reported.[663] The drug does not interfere with the exchange of respiratory gases in the blood or pulmonary tree.[664] While clinical experience in the treatment of glaucoma with acetazoleamide is still limited, it seems likely that the drug will prove a valuable addition to the armamentarium of the ophthalmologist.

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Correspondence

READING ADD

To the Editor:—When discussing with physicians the subject of reading adds, I have repeatedly been struck with the fact that, while the physician had a vague idea that the reading add caused some image magnification, he had no idea as to what images were being compared, or even roughly the extent of the magnification. The following remarks are designed to clarify these points.

The prime purpose of a reading add is to help provide a clear, focused retinal image when the accommodation is no longer able to do so. Its magnifying effect is only incidental and is due to the difference in power between an eye that accommodates and an eye that is aided by a convex lens. To make it specific: Say that the static eye has a power of + 58.00 D. To see clearly at 33.3 cm., it has to accommodate 3 D. and thereby increases its power to 61.00 D. If, instead of accommodating, the patient uses a + 3.00 D. lens as a reading add, the total power of lens and eye is still practically only + 58.00 D., for a lens placed at the anterior principal focus of the eye produces an optical system which has the same power as the eye alone. The lens merely changes the position of the cardinal points. Where a partial near correction of + 1.00 D. or + 2.00 D. is used, the total power of eye and lens is still practically + 58.00 D.

Let I_A stand for the clear retinal image of a near object produced by the accommodating eye, whose dioptral power we shall call D_A. Let I_B stand for the clear retinal image of the same near object produced by the action of both, eye and lens, and let the dioptral power of the combination be equal to D_B. Then it can be shown that $\frac{I_B}{I_A} = \frac{D_A}{D_B}$. The size of the images is inversely proportional to the respective powers. The latter statement is really correct only for objects at infinity. But where the focal lengths of the systems compared are very small in relation to the position of the object, we may also use this relation for a near object, as a first approximation.

From the above, we get from the reading add combined with the eye a larger, clear retinal image than would be obtained by the accommodating eye alone. Note that we are comparing the clear retinal image formed by the combination of eye and reading lens with the clear retinal image formed by the fully or partly accommodating eye. Taking the power of the eye as + 58.00 D., the magnification is about 1.6% per 1.00 D. This may be succinctly expressed by the relation $I_B > I_A$ by 1.6% per 1.00 D. of add. The correcting lens is assumed to be thin; so there is no "telescopic" effect.

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News and Comment

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

South Carolina Society of Ophthalmology and Otolaryngology and North Carolina Eye, Ear, Nose, and Throat Society.—A joint meeting of the North Carolina Eye, Ear, Nose, and Throat Society and the South Carolina Society of Ophthalmology and Otolaryngology will be held at Durham, N. C., Nov. 4, 5, and 6, 1954. Headquarters will be the Washington Duke Hotel.

Guest otolaryngologists will be Dr. Stanton A. Friedberg, of Chicago; Dr. James Maxwell, of Ann Arbor, Mich., and Dr. George Bayling, of Durham, N. C. The following guest ophthalmologists will likewise be on the program: Dr. Charles Iliff, of Baltimore; Dr. John McLean, of New York, and Dr. Townley Paton, of New York.

On Wednesday preceding the beginning of the meeting operative clinics will be held in the various hospitals of Durham and Chapel Hill.

Finally, there will be a football game on Saturday afternoon between the University of North Carolina and the University of South Carolina at Chapel Hill.

Society of Military Ophthalmologists and the Society of Military Otolaryngologists.—These societies will hold a joint dinner meeting at the time of the XVII International Congress of Ophthalmology and the annual meeting of the American Academy of Ophthalmology and Otolaryngology in New York City in September.

Dr. Frederick C. Cordes, Professor of Ophthalmology, University of California School of Medicine, will be awarded the plaque of honorary membership to the Society of Military Ophthalmologists at this meeting.

Cocktails and dinner will be served at 6 p. m. on Tuesday, Sept. 21, in the south and center lounges, Shelton Hotel, Lexington Ave. and 49th St., (across the street from the Waldorf-Astoria).

All members, ophthalmologists and otolaryngologists on active duty with the armed forces, are invited to attend. Application should be made to Col. J. H. King Jr., secretary-treasurer, Society of Military Ophthalmologists, Eye Clinic, Walter Reed Army Hospital, Washington 12, D. C.

Books

Transactions of the Pacific Coast Oto-Ophthalmological Society—1953. Pp. 349. Morrissey Brothers, 425 E. Pico St., Los Angeles.

The thirty-seventh annual meeting of the Pacific Coast Oto-Ophthalmological Society was held in Los Angeles on May 25 to 28, 1953. The papers presented in the Ophthalmological Section were as follows:

President's Address: The History of our Society.....C. Allen Dickey, M.D.

Some Remarks About Dizziness, Its Diagnostic Significance and Treatment.....William J. McNally, M.D.

Ocular Findings Frequently Diagnostic of Some General Diseases..Alston E. Braley, M.D.

Clinicopathologic Studies of Interesting Tumors of the Lid and Conjunctiva.....Merrill J. Reeh, M.D.

Complications of Cataract Surgery..... Carl D. F. Jensen, M.D.

Experiences with Retrolental Fibroplasia in Los Angeles County Hospital.....Warren A. Wilson, M.D.

Use of Sr^{90} Applicator in Beta-Ray Therapy of the Eye....Thomas C. Stevenson, M.D.

Cysts of the Iris, Ciliary Body, and Retina That Simulate Malignant Melanoma with Retinal Detachment.....Levon Garron, M.D.

Contamination of Fluorescein Solutions, with Special Reference to Pseudomonas Aeruginosa (Bacillus Pyocyaneous).....Daniel G. Vaughan, M.D.

Retinal Detachment Rates in a Specific Group.....Albert J. Brinckerhoff, M.D.

Disc Changes in Glaucoma.....A. Ray Irvine, M.D.

Some Aspects of Reading Problems in Children.....J. B. V. Butler, M.D., and M. R. Mongrain, M.D.

Round-Table Discussion

Treatment of Herpes Febrilis of the Cornea.....Panel: Alston E. Braley, M.D.; Levon Garron, M.D.; E. Merle Taylor, M.D.; Edward S. Murphy, M.D.; Dohrmann Pischel, M.D.

Hereditary Hemorrhagic Telangiectasia.....David A. Dolowitz, M.D.; O. N. Rambo Jr., M.D.; F. E. Stephens, Ph.D.

Transactions of the American Ophthalmological Society, 1953. Volume 51, Editor, Gordon M. Bruce, M.D. Price, $18.00. Pp. 793. Columbia University Press, 2960 Broadway, New York 27, 1954.

The Eighty-Ninth Annual Meeting of the American Ophthalmological Society was held at Hot Springs, Va., on May 28, 29, and 30, 1953, with Dr. William L. Benedict, President, occupying the Chair. The "Transactions" include the proceedings, the papers presented, and their discussions, and the theses which have been accepted from the newly elected members.

The papers and theses, by title, are listed as follows:

A Preliminary Report of an Ophthalmic Survey on a Mass Population in Southern Rural Mississippi. William B. Clark, M.D.
James H. Allen, M.D.
Edmund L. Leckert Jr., M.D.
Robert F. Lorenzen, M.D.
Y. L. Wang, M.D.

Cystine Crystals in the Cornea and Conjunctiva.
Everett L. Goar, M.D.
G. Walter de la Motte, M.D.

A Further Report on the Effect of Dicumarol on the Visual Fields in Glaucoma.
William P. McGuire, M.D.

Notching of the Optic Chiasm by Overlying Arteries in Pituitary Tumors.
C. Wilbur Rucker, M.D.
James W. Kernohan, M.D.

Retraction Nystagmus: A Case Report.
Donald J. Lyle, M.D.
Frank H. Mayfield, M.D.

Ocular Signs of Wernicke's Disease.
David G. Cogan, M.D.
Maurice Victor, M.D.

Glioma of the Optic Nerve as a Manifestation of von Recklinghausen's Disease.
Don Marshall, M.D.

A Brief Account of Baron Wenzel's Operation for the Extraction of Cataract, with an Exhibition of Such Instruments As Were Used.
Burton Chance, M.D.

Essential Atrophy of the Iris: A Histopathologic Study.
Parker Heath, M.D.

A Modified Krönlein Operation.
Raynold N. Berke, M.D.

Studies in Experimental Ocular Tuberculosis: XVII. Effects of Isoniazid in the Normal Nonimmune Rabbit.
Alan C. Woods, M.D.
Bernard Becker, M.D.
Ronald M. Wood, M.D.

The Stellar Figure in the Macular Region.
Arthur J. Bedell, M.D.

Clinical Studies of the Myopic Macula.
Ralph I. Lloyd, M.D.

Studies on the Mechanism of Lens Injury in Radiation Cataract.
Irving Puntenney, M.D.
David Schoch, M.D.

Metabolism of the Lens and the Occurrence of Cataract.
P. J. Leinfelder, M.D.

Occurrence of Cystoid Spaces in the Lens.
Algernon B. Reese, M.D.
Joseph A. C. Wadsworth, M.D.

Gonioscopy in the Diagnosis of Tumors of the Iris and Ciliary Body, with Emphasis on Intraepithelial Cysts.
Harold G. Scheie, M.D.

Glandular Type Exophthalmos: Methods of Treatment, Including Radioactive Iodine.
A. D. Ruedemann, M.D.
K. E. Corrigan, M.D.

Uptake of Radioactive Phosphorus by Intraocular Neoplasms.
Edwin B. Dunphy, M.D.
Knud K. Dreisler, M.D.
John B. Cadigan, M.D.
William Sweet, M.D.

Treatment of Cysts of the Iris with Diathermy Coagulation.
Derrick Vail, M.D.

Pseudoexfoliation of the Lens Capsule: Relation to True Exfoliation of the Lens Capsule As Reported in the Literature, and Role in the Production of Glaucoma Capsulocuticulare.
Georgiana Dvorak-Theobald, M.D.

Improved Scissors for Enlargement of Cataract Incision.
Ramón Castroviejo, M.D.

Visual Field Examination by a New Tachistoscopic Pattern Method: A Preliminary Report.
David O. Harrington, M.D.
Milton Flocks, M.D.

THESES

X-Ray Treatment of Uveitis.
Moacyr E. Alvaro, M.D.

The Eye in Experimental Arteriosclerosis.
Justin M. Donegan, M.D.

The Eye and Ocular Adnexa of the Monotreme Ornithorhynchus Anatinus.
Frank W. Newell, M.D.

Spontaneous Regression in Retrolental Fibroplasia.
William C. Owens, M.D.

Corneal Transplantations: A Review of 365 Operations.
R. Townley Paton, M.D.

The Endothelium of the Cornea and Its Clinical Implications.
Frederick W. Stocker, M.D.

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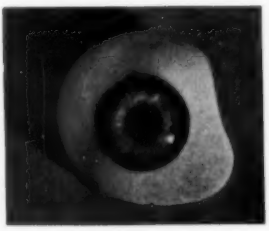

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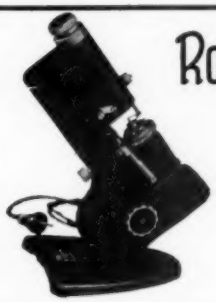

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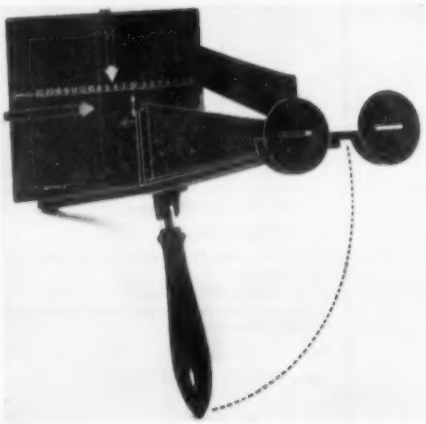

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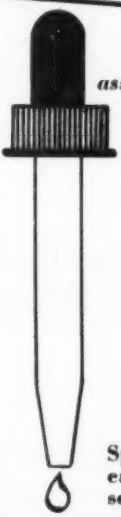

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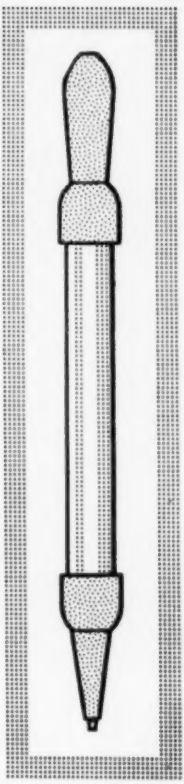

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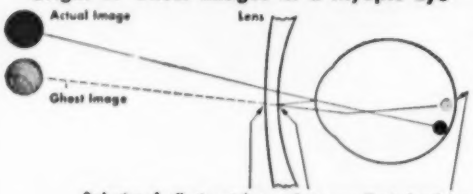

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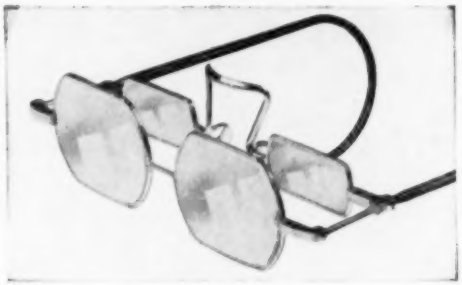

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RAPID ACTION

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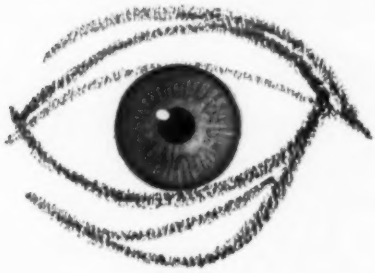

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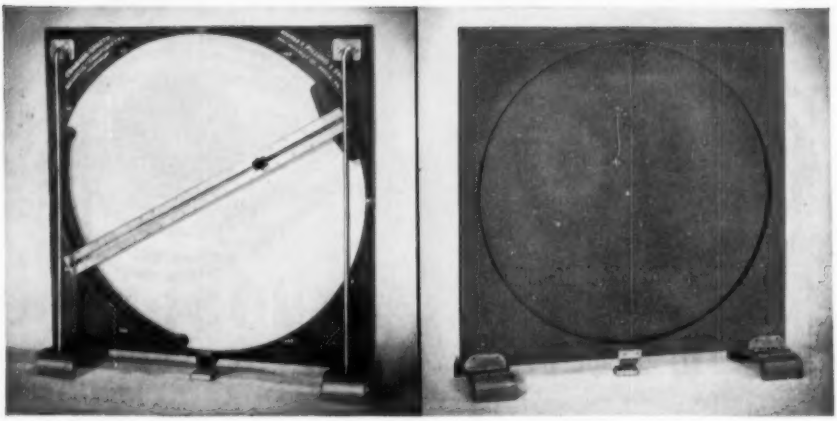
1. Gettes, B. C., and Leopold, I. H.: A. M. A. Arch. of Ophth. 49:24 (Jan.) 1953.
2. Stolzar, I. H.: Am. J. Ophth. 36:110 (Jan.) 1953.



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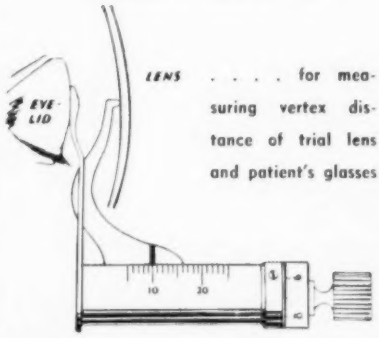

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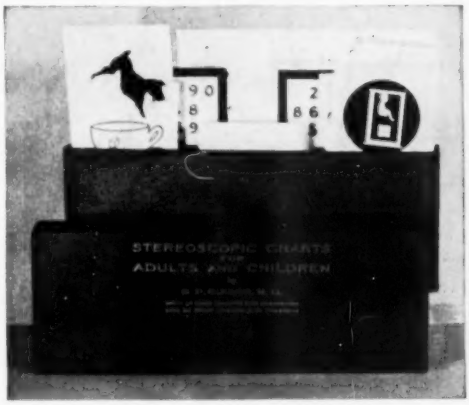

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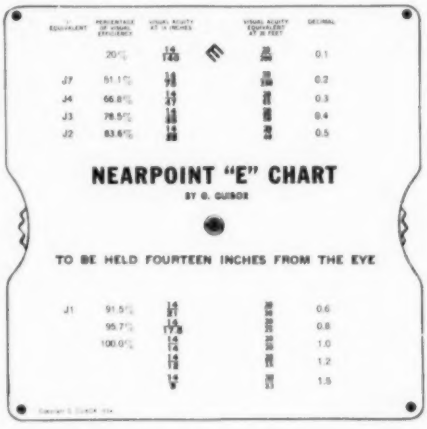

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